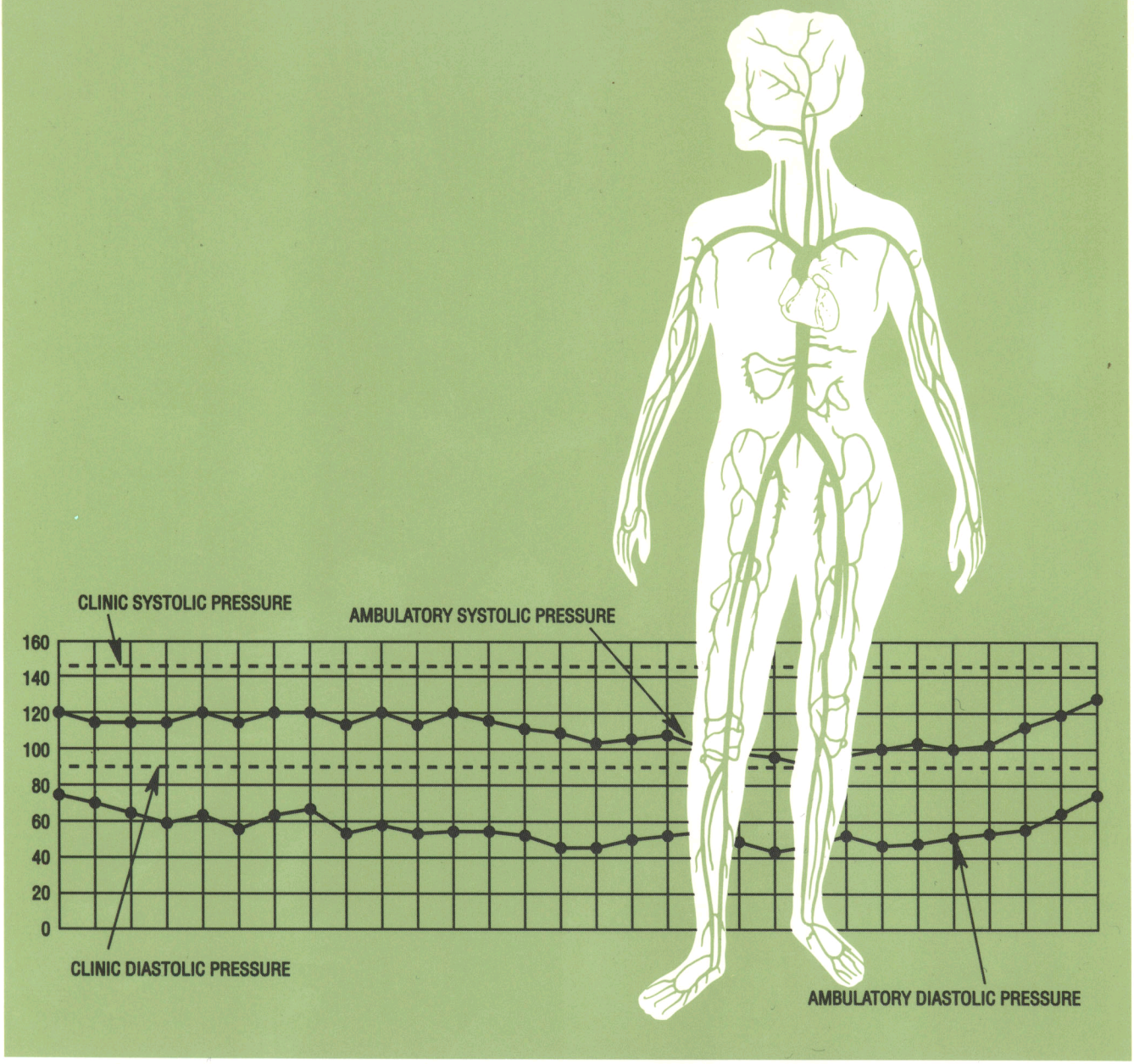
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BIOPHYSICAL MEASUREMENT SERIES

AMBULATORY BLOOD PRESSURE



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PREFACE

1994 American College of Cardiology Position Statement:

"The Hypertensive Diseases Committee of the American College of Cardiology now recommends ambulatory blood pressure monitoring as a mature, clinically applicable (useful) technology for the management of selected hypertensive patients. Standards for ambulatory blood pressure have been developed by the Associations for the Advancement of Medical Instrumentation and the British Hypertension Society and are available. American and international consensus meetings have also developed clinical indications and guidelines for this procedure."[1]

[1]Sheps SG, Pickering TG, White WB, et al. Ambulatory Blood Pressure Monitoring. *JACC.* 1994;23:1511-1513.

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INTRODUCTION

The measurement of blood pressure is one of the most important procedures in clinical medicine, and also one of the most unreliable. The primary reasons for this are the inherent inaccuracy of the standard auscultatory method, observer error, and error arising from the spontaneous or induced variations of blood pressure.

It has been recognized for over 50 years that the conventional clinic measurements of blood pressure may not be all they seem, and often give only a very poor representation of an individual's average or true level of blood pressure. Although the technique of ambulatory blood pressure (ABP) monitoring was invented more than 30 years ago, it is only now beginning to find acceptance as a clinical tool for the routine evaluation of hypertension and related conditions. The rationale underlying the use of ambulatory monitoring is very simple: blood pressure varies. Both the level of blood pressure and its variations are of interest, and these can only be described adequately by taking large numbers of measurements in the patient's everyday surroundings. Currently available ABP monitors enable this to be done reliably and with very little inconvenience to the patient.

This book will cover general issues of ABP monitoring, such as how ABP monitors work, how they are tested for accuracy, when they should be used, and how data should be interpreted. In addition, a chapter is included on how to implement an ABP monitoring program. ABP monitoring is a rapidly evolving field, and there is significant disagreement on some issues. Whenever possible, we have attempted to present all sides of an issue.

The reference list is not meant to be exhaustive, only representative or key references on each topic are included.

1.0 AMBULATORY BLOOD PRESSURE: AN OVERVIEW

1.1 History of Ambulatory Monitoring

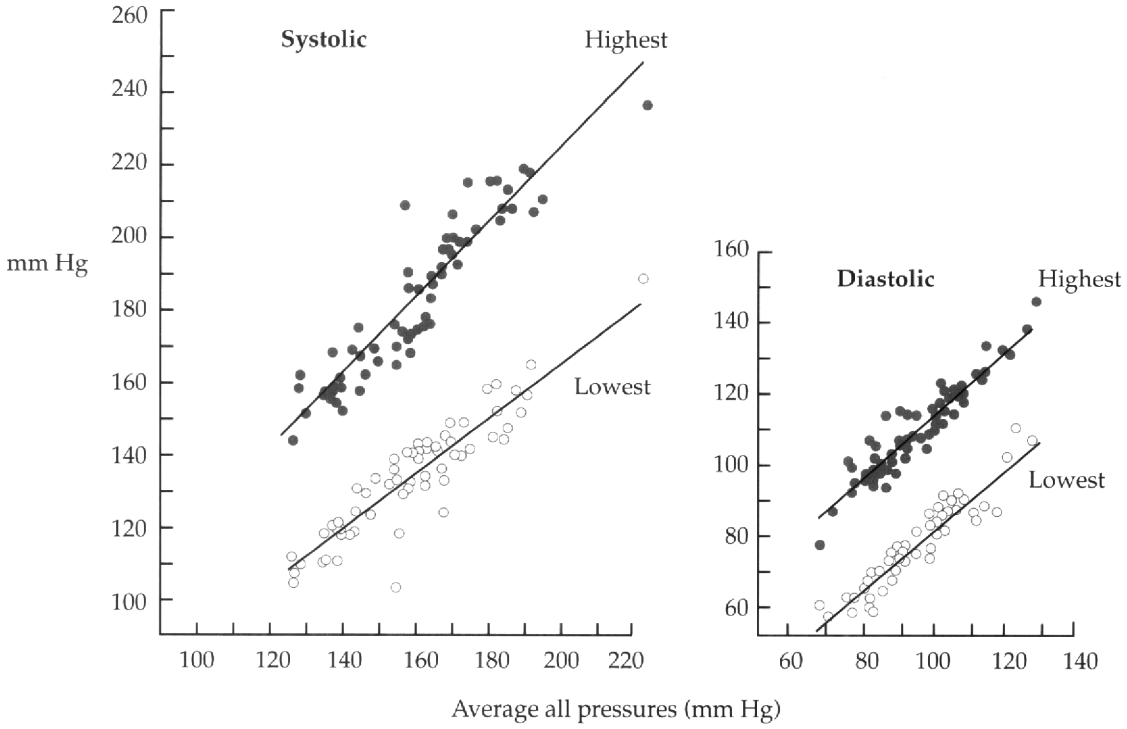
The early development of ambulatory monitoring was pioneered by Dr. Maurice Sokolow, who in the 1950s became the head of the hypertension section of San Francisco General Hospital. He carried out one of the first prospective studies of hypertensive individuals, in the days when effective antihypertensive drugs were only just becoming available. His study, like others after it, showed that the risk associated with hypertension was proportional to the height of the blood pressure; but one of the puzzling findings was that there were many persons with apparently very high pressures who lived a normal life span, and others with only modest elevations who died from cardiovascular complications at an early age. He suspected that one reason for this was that the clinic pressures in these patients were not representative of their pressures during everyday life, and that if it was possible to measure these pressures they might give a better estimate of the patients' risk. He enlisted the help of two of his colleagues, one an internist and one a physicist, who devised a design for a monitor. They then approached the president of Remler Corporation, a small electronics manufacturing company, who agreed to manufacture the monitor. It operated on the Korotkoff sound principle, and detected the sounds from a microphone placed over the brachial artery, under a sphygmomanometer cuff. The cuff had to be inflated manually by the patient. In its first version, the monitor consisted of two units attached to a belt and one worn on each hip. It was crude, but it worked; a later version had only one unit.

A series of classic papers resulting from the initial use of this device have formed the groundwork for much of the later research in the subject of ambulatory monitoring.[1-3] The first of these described the early version of the recorder, which was relatively bulky and required the patient to inflate the cuff manually.[1] The second paper described the application of the recorder in hypertensive patients.[2] It included a photograph of a young woman wearing the recorder, which consisted of two cases (one worn on each hip), a cuff and inflating bulb, and a pair of signal lights clipped to the subject's blouse to indicate when she should take a reading. By today's standards, this was a very cumbersome device, but it provided excellent data. This paper established the enormous variability of blood pressure during the day (sleep recordings were, of course, impossible to take) as shown in Figure 1.1. It also demonstrated that clinic pressures tend to be higher than ambulatory pressures in the majority of patients.

A third paper, published in 1966, showed that ambulatory pressures recorded over 2 to 3 days correlated more closely with target organ damage than casual pressures.[3] This relationship was closer for the average level of pressure than either the highest of the lower readings. This paper provides the cornerstone of the evidence that ambulatory recordings may have greater clinical validity than casual readings.

Dr. Sokolow described his subsequent attempts to improve on the design of the monitor as follows: "Some years ago Dr. Hinman talked to a number of Japanese electronics firms, as well as some of the first in the U.S., trying to persuade them to make an automatic apparatus to automate decoding, to decrease the size of the recorder, and to make other improvements. Each firm said it would cost more than $1 million

Figure 1.1 — The range of blood pressure (highest and lowest) occurring during the day as a function of the overall level of pressure.

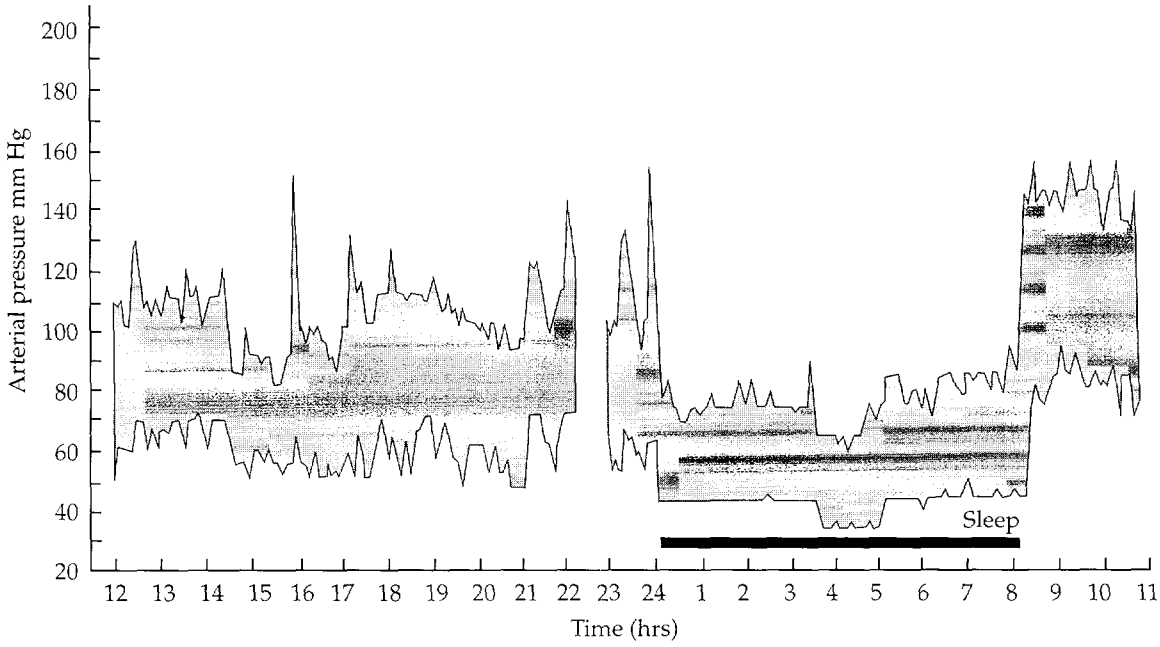


to design such an apparatus. The National Institute of Health (NIH) subsequently issued a request for proposals to develop such an apparatus; none was awarded because the minimum estimated cost was $1 million. During this time, NASA came to us and used our Remler apparatus to determine the blood pressure in astronauts during flight."[4]

At the same time work was being conducted in San Francisco, Dr. Frank Stott at Oxford University in England was developing a noninvasive recorder that was fully automatic and, hence, could measure blood pressure changes during sleep. This machine, which was not portable but could be wheeled to a patient's bedside, also demonstrated the large spontaneous variability of blood pressure over a 24-hour period. Rather than developing a noninvasive ambulatory recorder, Stott took the bold move of producing an intra-arterial recorder. This device, which was the forerunner of the Oxford Medilog recorder, measured pressure using a nylon catheter placed in the brachial artery. The arterial pressure trace was recorded with a light galvanometer, on film, and the catheter was perfused with heparinized saline from a chamber pressurized with cigarette lighter fluid. This work resulted in another classic paper by Bevan, Honour, and Stott in 1969.[5] Figure 1.2, reproduced from this paper, shows the diurnal rhythm of blood pressure in a normal subject.

After this there was further work done on the phenomenology of blood pressure variability using the intra-arterial technique, which was generally regarded as a rather esoteric research tool. The pioneering work of Sokolow's group with the noninvasive method was not followed up during the 1970s, even though the Remler

Figure 1.2 — Diurnal blood pressure profile of a normal subject obtained with intra-arterial ambulatory monitoring.



recorder was commercially available. At the end of the 1970s, Del Mar Avionics introduced the first fully automatic noninvasive monitor, the Pressurometer II (which was actually no less bulky and no more reliable than the Remler monitor). The original development of this device was carried out by William Thornton, an electrical engineer who, at that time, was preparing to go to medical school. After he completed his medical training he worked for NASA and wore the Del Mar monitor on one of the earliest Space Shuttle flights. Since that time there has been a dramatic increase in the variety and number of noninvasive recorders available, spurred on partly by developments in technology, but also by increasing concerns that the mass treatment of mild hypertension is no panacea.

1.2 Rationale for the Clinical Use of Ambulatory Monitoring: Prediction of Morbidity

If ambulatory monitoring is to be accepted as a clinically useful tool it must provide a better prediction of cardiovascular morbidity than other measures. There are two ways to support this idea. The ideal way would be to show that ambulatory pressure predicts cardiovascular morbid events better than clinic pressure. While this is scientifically desirable, in practice it is very difficult to achieve because it is difficult to perform natural history studies in hypertension and because large numbers of patients need to be followed for many years. The other way is to use a surrogate measure for morbid events: this can be done either cross-sectionally or longitudinally, and has the advantage of requiring smaller numbers of patients followed over a shorter period of time. Several surrogate measures have been used, the most popular of which has

been left ventricular hypertrophy (LVH). Not surprisingly, there are many more studies relating ambulatory pressure to target organ damage than to morbidity.

1.2.1 Ambulatory vs. Clinic Blood Pressure and the Prediction of Target Organ Damage

The typical design of studies of the relationship between ABP and target organ damage has been to measure ambulatory and clinic pressure in a group of patients with varying levels of blood pressure, and to determine which measure of blood pressure correlates most closely with the degree of target organ damage. Most studies have used a single measure of target organ damage, although a few have used aggregate measures. There are more than 20 studies in the literature showing closer correlations between ABP and target organ damage than between clinic pressure and target organ damage.[4] The most widely used index of damage has been left ventricular hypertrophy measured by the echocardiogram, but others have been ECG-LVH, microalbuminuria, cerebrovascular disease measured by magnetic resonance imaging (MRI), and arterial distensibility.[6-12]

1.2.1.1 Aggregate Measures of Target Organ Damage

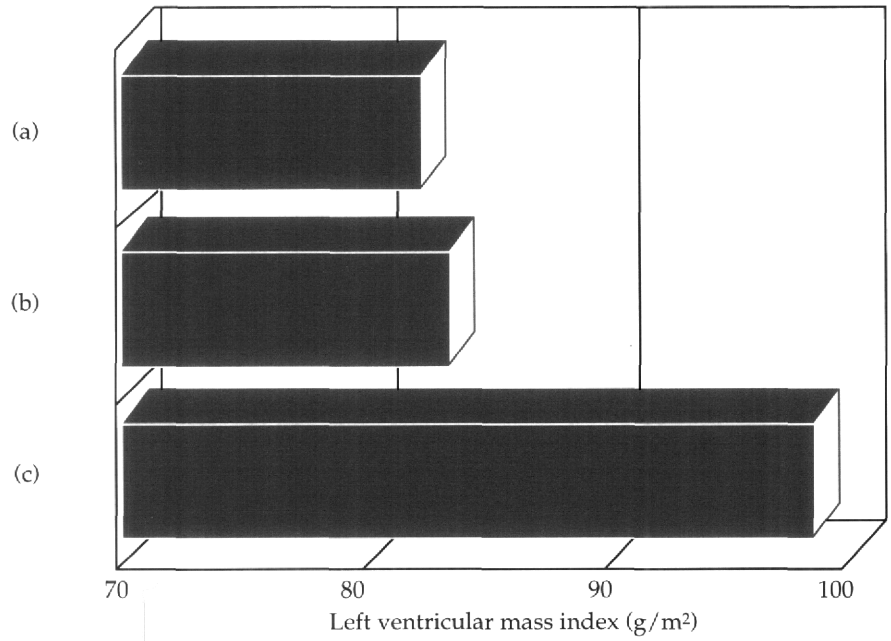
The first study relating clinic and ambulatory pressure to target organ damage was the classic paper by Sokolow et al. in which three measures were used: LVH evaluated from the ECG, heart size from the chest x-ray, and fundal changes.[3] This aggregate measure of target organ damage was more closely related to ambulatory daytime blood pressure (r=0.63 for systolic and 0.65 for diastolic) than to clinic pressure. A similar composite index of target organ damage was used in a more recent study by Parati et al. who also found a closer correlation between target organ damage with ambulatory (in this case, 24-hour) blood pressure than with clinic blood pressure.[13]

1.2.1.2 Left Ventricular Hypertrophy

Left ventricular hypertrophy has traditionally been evaluated by the ECG, although echocardiography has the advantage of being both more sensitive and more specific. Thus, the prevalence of LVH by ECG criteria may be as low as 5% in patients with mild hypertension, while by echocardiographic criteria it may be between 20% and 50%.[14] The importance of LVH as an independent predictor of morbidity is now well established.[15,16]

The results of studies relating clinic and ABP to LVH are summarized in Table 1.1. Most have used echocardiographically determined LVH (expressed as LV mass). All the studies shown in the table found a closer correlation for ambulatory than clinic blood pressure with LV mass, with one exception; but even here measures of interventricular septal and posterior wall thickness were more closely related to ambulatory than to clinic pressure. Verdecchia et al. analyzed their data in a different manner — by computing the regression line relating clinic to ambulatory pressures.[7] Patients whose ABP was high relative to their clinic pressure were much more likely to have LVH than those whose ABP was low.

Figure 1.3 — Left ventricular mass index in three groups of subjects: (a) normotensives; (b) hypertensive dippers (normal nocturnal fall of pressure); and (c) hypertensive nondippers (pressure remains high).



It has also been found that the correlation between ABP and LVH is closer when pressure is measured on a work day, rather than a nonwork day. This raises the possibility that intermittent elevations of pressure, such as those that occur during working hours, may be important in the development of LVH.[6]

While most studies have found slightly higher correlations for daytime than for nighttime blood pressures with LVH (Table 1.1), there is also some evidence that patients whose blood pressure remains elevated during the night have more LVH than those whose pressure shows the normal decrease (see Figure 1.3).[17]

These apparently conflicting results may be resolved as follows: In the majority of subjects, blood pressure falls at night by approximately the same degree, so that most of the inter-individual variation of 24-hour blood pressure will be determined by differences of daily activity and, hence, better correlations will be obtained between daytime pressure and LVH (on the assumption that it is the average or 24-hour level of pressure that determines LVH). If, however, the population being studied contains a significant portion of individuals whose pressure remains high at night (nondippers), the correlation may be closer for nighttime pressure.

The better correlation with ambulatory than with clinic pressure can be attributed to a combination of two factors. First is the effect of the greater number of readings. This was elegantly demonstrated in a study by Prisant et al. who showed not only that the correlations between clinic pressure and LVH were stronger if multiple clinic readings were used (rather than a single one), but also that they were weaker if a subset of ambulatory readings (e.g., from 8:00 a.m. to 12:00 p.m.) were used rather than the average for the full 24 hours.[18] The second factor is the more representative nature of the ambulatory readings.

Table 1.1 – Correlations Between Different Measures of Blood Pressure and Target Organ Damage

Organ	Measured Variable	Author	N	Reference	Correlation Coefficient: Clinic SBP	Ambulatory Daytime	SBP Nighttime
Heart	ECG LVH	Vermeersch	180	8	0.19	0.36	–
		Cox	216	23	0.38	0.27	0.31
	Echo LVH	Rowlands	50	24	0.51	0.57	0.56
		Drayer	12	25	0.55	0.82	0.70
		Devereux	100	6	0.24	0.50	0.10
		Antivalle	84	26	0.26	0.45*	–
		Gosse	61	27	0.40	0.53	–
		White	47	28	0.55	0.61	0.58
		Verdecchia	237	17	0.38	0.40	0.47
		Palatini	42	29	0.52	0.62*	–
		Prisant	55	18	0.32	0.59*	–
		Moulopoulos	40	30	0.39	NS	NS
		Baba	17	31	-0.22	-0.07**	0.15
		Marabotti	29	32	0.38	0.27	0.31
		Bauwens	35	33	0.08	0.34*	–
		Kuwajima	49	34	0.14	0.24	0.43
		Pearce	29	35	0.38	0.38	0.25
		Rizzoni	91	36	0.25	0.44*	
Kidney	Albumin Excretion	Opsahl	42	9	0.31	0.44*	–
		Dimmitt	25	37	0.60	0.52	–
	NAG Excretion	Opsahl	42	9	0.14	0.32*	–
Arteries	Pulse Wave Velocity	Asmar	22	12	0.24	0.68	–
Combined	ECG, CXR, Fundi	Sokolow	124	3	0.48	0.63	–

** 24-hour average SBP used*
*** Correlations with LV wall thickness: work pressure used for daytime value*
N=number of subjects; NAG = N-Acetyl-Glucosaminidase; NS = Not significant

1.2.1.3 Left Ventricular Filling

Abnormalities of left ventricular diastolic performance have recently become popular as possible early markers of the effects of hypertension on the heart, and can be investigated either by radionuclide ventriculography or by echocardiography. An important point, however, is that filling abnormalities are just as likely to be determined by functional as by structural changes, which may limit their usefulness as markers of target organ damage. Thus, they are likely to be less stable over time than LVH.

One study has related clinic and ABP to diastolic filling abnormalities in normotensive and never-treated hypertensive subjects.[19] The most potent determinant of filling rate was found to be age, followed by ABP. Below the age of 55, normotensives had a higher filling rate than hypertensives, but in older subjects it was uniformly depressed. There was less correlation between blood pressure and filling rate for clinic than for ABP.

1.2.1.4 Microalbumin Excretion

An increased rate of albumin excretion by the kidney may be one of the earliest detectable renal changes in hypertension, and ABP has reported to show a better correlation with microalbuminuria than clinic pressure.[9] Albuminuria has also been found to be associated with a diminished nocturnal fall of blood pressure, as described in Section 4.1.2.[10]

1.2.1.5 N-Acetyl-Glucosaminidase Excretion

The N-Acetyl-Glucosaminidase (NAG) enzyme is formed in renal tubules and is detectable in the urine. It is found in increased quantities in hypertensive patients, although it may not be a very specific marker for the effects of blood pressure on the kidney. Nevertheless, Opsahl et al. reported a closer correlation between NAG excretion and ABP than with clinic pressure.[9]

1.2.1.6 Arterial Stiffness

Increased arterial stiffness occurs in hypertension as a result of pressure-induced hypertrophy of the arterial wall, and it may also be a contributory factor in the development of systolic hypertension. One study has reported that pulse wave velocity (an indirect measure of arterial stiffness) correlated more closely with ABP than with clinic pressure.[12]

1.2.2 Ambulatory vs. Clinic Pressure and the Prediction of Morbidity

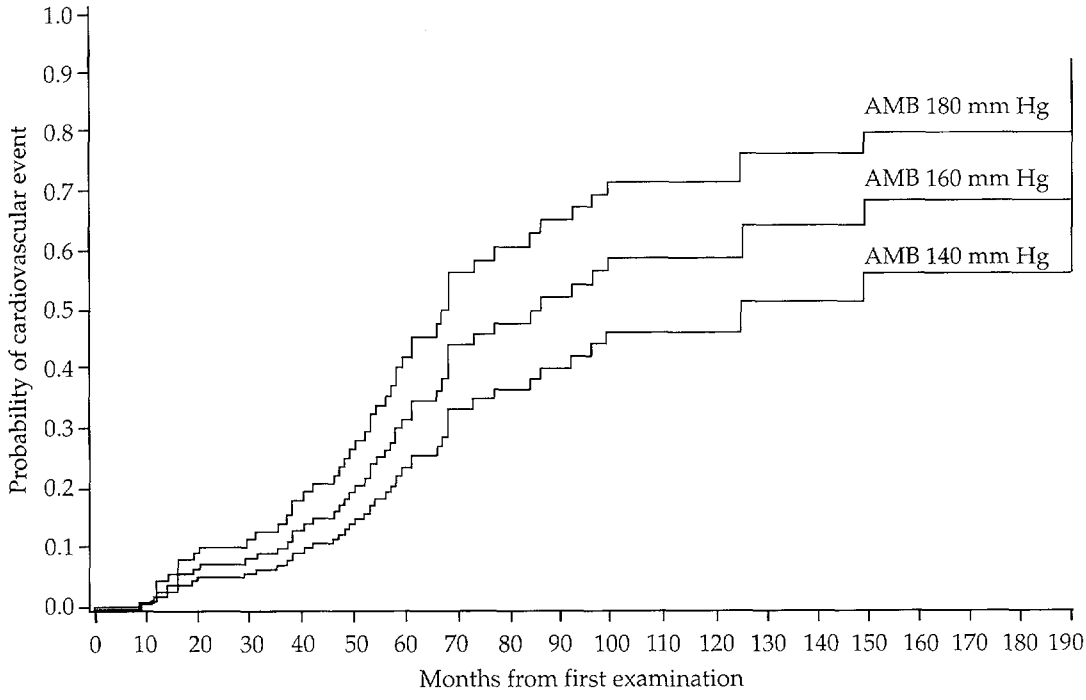
From the point of view of both the clinician and the research scientist, the superior ability of ABP as compared to clinic pressure in predicting cardiovascular morbidity is crucial to the validity of the technique. Evidence for this rests largely on one prospective study, conducted by the pioneers of ambulatory monitoring, Perloff and Sokolow. Three major papers were published from this study. In the first, Perloff et al. analyzed the data of 1,076 patients followed for an average duration of five years.[20] Ambulatory and clinic pressures were significantly correlated with each other, although ABP was on average 16/9 mm Hg lower. Patients were classified according to whether their ABP was high or low relative to their clinic pressure. Those with higher ABP had a higher mortality and incidence of cardiovascular morbidity than those with lower ABP. Ambulatory pressure had the greatest predictive value in patients who were less than 50 years old, whose diastolic pressure at the time of entry to the study was less than 105 mm Hg, and who had suffered no prior cardiovascular event.

Ambulatory pressure was not helpful in defining the prognosis of patients with more severe hypertension, however.

A second paper used the same data, but a much more sophisticated analysis using the Cox Proportional Hazards Linear Regression model to control for the influence of other predictor variables.[21] Seven hundred and sixty-one patients met the study criteria, with an average follow-up period of 66 months. Ambulatory blood pressure was expressed both as the predicted and the residual level. The former was derived from the regression equation relating clinic and ABP for all the patients, and the latter obtained by subtracting the predicted level from the observed value. Separate life-table analyses were run for 659 patients who had no previous cardiovascular event (i.e., renal failure or angina) and for the 102 patients who had. The predictor variables included in the analysis were ambulatory and clinic pressures, age, sex, ECG-LVH, retinopathy, and use of antihypertensive therapy. For patients with no previous event the significant predictors were age, sex, ECG-LVH, and predicted and residual ABPs. For those with a previous event, the predictors were age, sex, antihypertensive treatment, and residual ambulatory pressures. As shown in Figure 1.4, the morbidity was lower in patients whose ABP was low in comparison to clinic pressure. Thus, unlike the earlier analysis which indicated that ABP added to the prognostic ability of clinic pressure only in patients who had no previous cardiovascular event, the Cox model analysis showed that ABP was also of value in patients with a previous event.

The third paper analyzed the findings in a subgroup of 459 patients who were taking antihypertensive medications when first studied.[22] As in the earlier analysis, patients whose ABP was lower than expected from their clinic pressure were at lower risk of morbidity than those with higher ABP.

Figure 1.4 — Cumulative probability of a cardiovascular morbid event plotted according to the original level of ambulatory pressure.



2.0 PHYSIOLOGY AND SIGNIFICANCE OF BLOOD PRESSURE LEVEL AND VARIABILITY

2.1 Physiology of Blood Pressure

The pulsatile nature of arterial blood pressure is determined by a combination of the properties of the left ventricle pumping the blood and of the arterial system into which the blood flows. Four measures of blood pressure are used for clinical purposes: systolic, diastolic, mean, and pulse pressure. The traditional equation relating blood pressure to the function of the heart (cardiac output) and arterial system (peripheral resistance) may be expressed as:

Blood pressure = cardiac output x peripheral resistance

This applies to the mean arterial pressure, because on an analogy with Ohm's law of electricity (voltage = current x resistance) it describes the steady-state, or direct current.

The mean arterial pressure is the average or integrated level of pressure over time, and can be measured as such by direct intra-arterial recording, or be estimated indirectly from the conventional Korotkoff sound method or, directly from the oscillometric method.

2.1.1 Arterial Pressure Wave and Determinants of Systolic, Diastolic and Mean Pressure

The dynamic nature of arterial pressure requires that any mathematical description of it treats it as an oscillating pressure wave, or, to use the analogy with electricity, as alternating current where impedance replaces resistance. The simplest model of the arterial tree is the "Windkessel", which can be likened to an expandable chamber (the large arteries) into which the heart pumps, with a narrow outlet of variable resistance (the arterioles).[38] In this model, an increase in the peripheral resistance will raise the level of mean arterial pressure without altering the shape of the pressure wave, while a decrease in compliance will raise the pulse pressure without altering the mean pressure. Ventricular ejection (stroke volume) is the other major determinant of the pulse pressure (Figure 2.1).

This model does not take into consideration the other major determinant of the shape of the pressure wave, which is wave reflection from the periphery. The effects of this are shown schematically in Figure 2.2, in which the arterial tree is considered as a tube with a partially closed end from which the incident pressure wave is reflected. The normal waveform (Figure 2.2a) has a secondary diastolic wave after the incisura, which is attributable to wave reflection from the peripheral end of the tube. When the compliance of the tube is reduced the pulse pressure is increased (Figure 2.2b). However, the decreased compliance will also increase pulse wave velocity, so that the reflected wave will return to the central circulation sooner, and will now aug-

Figure 2.1 — The major determinants of the static (mean pressure) and dynamic (pulse pressure) components of the arterial pressure wave.

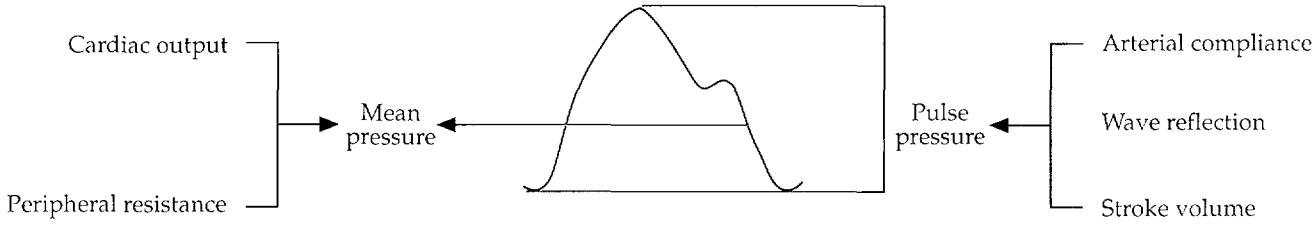
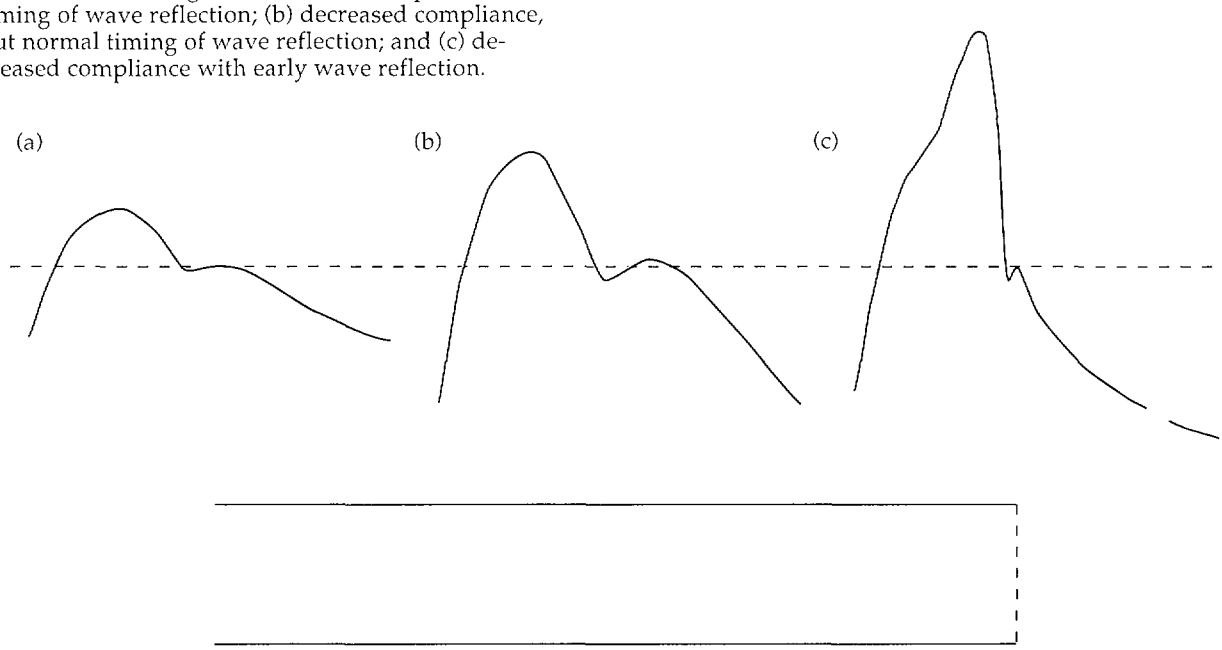


Figure 2.2 — Hypothetical pressure waves at the input of a tubular model of the arterial tree, shown at the bottom of the figure: (a) normal compliance and timing of wave reflection; (b) decreased compliance, but normal timing of wave reflection; and (c) decreased compliance with early wave reflection.



ment the pressure wave before the incisura, as shown in Figure 2.2c. The net effect of this is to produce a late systolic peak, which is a characteristic feature of the arterial pressure waveform in hypertensive individuals and in elderly normotensives.[39]

A more mathematical description of these phenomena is to regard the pressure wave as having two major determinants: ventricular ejection and input impedance. The latter may be regarded as the dynamic component of the peripheral resistance and is itself determined by the two dynamic factors described above — arterial compliance and wave reflection.

Progressive changes occur as the wave proceeds to the peripheral circulation, with an increase of pulse pressure and the maximal rate of rise (dp/dt). Mean pressure changes very little and there is an increase of systolic pressure and a slight decrease of diastolic pressure.[40] For example, for a person with an aortic pressure of 122/81 mm Hg, the corresponding pressure might be 131/79 mm Hg in the brachial artery and 136/77 mm Hg in the radial. These two sites are the ones most commonly used for intra-arterial recording. The relationship between peripheral (radial) and central (aortic) pulse pressure is similar during rest and exercise (the radial pulse pressure being about 46% greater than aortic in both conditions), but not during upright tilt, when the radial pulse pressure may be 65% greater than in the aorta.[41]

The increased systolic pressure in more peripheral arteries is a consequence of peripheral wave reflection, with a summation of the incident and reflected waves. The systolic pressure gradient between central and peripheral arteries may be less marked in older and more hypertensive subjects, because the stiffer arteries conduct the pulse wave quicker and more effectively so that the augmentation of the systolic peak by the reflected wave in the more central arteries is more pronounced.[38,39] Since arterial stiffness is partly dependent on vascular tone, it changes in different situations, with the result that the relationship between central and peripheral systolic pressure can also change.

2.1.2 Clinic Blood Pressure

The clinic, office, or casual blood pressure, as it is variously termed, is the traditional measurement by which physicians have characterized an individual's level of pressure. The measurement is almost always made with a mercury sphygmomanometer, and the number of readings typically varies from one to three. Recommendations as to how clinic blood pressure should be measured have been published by organizations such as the American Heart Association and British Hypertension Society.[42,43] Some of the technical issues are discussed in Section 10.1.4.

2.1.3 True Blood Pressure

True blood pressure is a conceptual rather than an actual measurement, and is the average or usual level of pressure for a particular individual at a given site. Its importance is that it is the true blood pressure which is supposedly related to cardiovascular morbidity, and the clinic pressure may be regarded as a surrogate measure of it. Since blood pressure is continually varying, true blood pressure is best estimated by taking the average of a large number of readings rather than by relying on one or two. The slope of the line relating blood pressure and morbidity is steeper for true blood pressure than for clinic pressure.[44]

2.1.4 Ambulatory Blood Pressure

Ambulatory blood pressure can be defined as a reading or readings taken during normal daily activities. Such readings are normally taken by ambulatory monitors, typically over 24 hours at intervals of 15 to 30 minutes, and the results expressed as the average level over the day, the night, or the entire 24 hours.

2.1.5 Intra-Arterial Blood Pressure

The intra-arterial pressure is the blood pressure recorded directly from a large artery such as the aorta, brachial, or radial artery. Such readings form the "gold standard" by which other techniques of blood pressure measurement are compared, although they are not used for the routine clinical evaluation of hypertension. Refer to the Biophysical Measurement book entitled *Blood Pressure* for a discussion of the factors that influence measurement accuracy in invasive and noninvasive blood pressure.

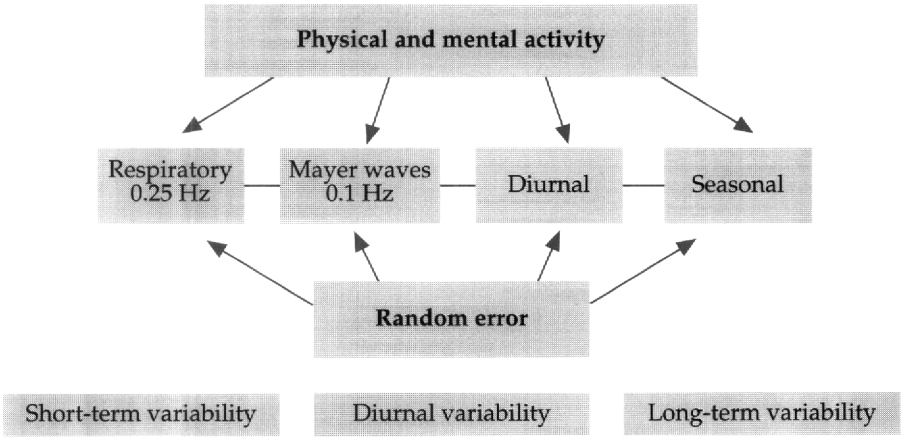
2.2 Physiology of Blood Pressure Variability

Blood pressure variability is a term that is often used rather loosely, as if it were a single entity that could be adequately described by a single number. In fact, it encompasses a number of sources of variation with different time courses ranging from a few seconds to a year, and with quite different origins (see Figure 2.3). For the sake of simplicity, it can be divided into three categories: short-term variability, with a periodicity of seconds and minutes; diurnal variability, with a periodicity of 24 hours; and seasonal variability, with a periodicity of 1 year.

Variability is a quantitative concept, and the way in which it is expressed will have a major effect on the numbers that are obtained. Short-term variability, as measured over periods of up to 1/2 hour or so, will be influenced largely by respiratory variations and Mayer waves, and by changes in physical and mental activity. Diurnal variability is typically expressed as the day-night or sleep-wakefulness difference, and is determined largely by changes in arousal and activity, but also by endogenous influences. Seasonal variations are expressed as winter-summer differences, and are thought to be determined by environmental temperature changes.

Another important consideration is the choice of an absolute as opposed to a relative measure of variability. The classic example of the former is the standard deviation (in this case expressed as mm Hg) and of the latter the coefficient of variation (the standard deviation expressed as a percentage of the average level). Which is more appropriate has been the subject of considerable debate.

Figure 2.3 — The principal types of blood pressure variability and their sources.



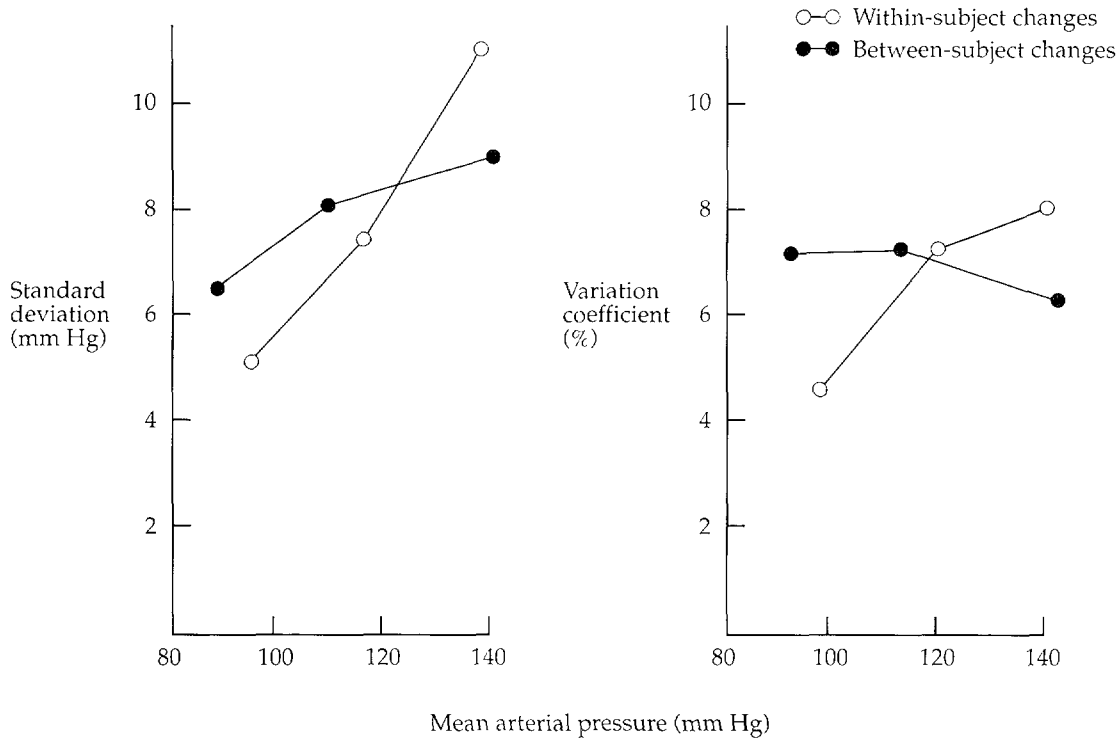
Another factor that will influence the estimate of variability is the set of circumstances in which the measurements were made. In the same subject, very different measures of variability will be obtained depending on whether the subject is resting quietly or physically active. An extreme example of this is patients with autonomic failure (see Section 4.0), whose blood pressure variability is greater than normal while they are active during the day, but whose nocturnal blood pressure decrease is smaller than normal. Therefore, in active subjects, such as are commonly studied by ambulatory monitoring, a case can be made for normalizing the blood pressure variability to the activity of the subject.

2.2.1 Spontaneous Short-Term Variability

As shown schematically in Figure 2.3, a number of discrete sources of blood pressure variability can be identified. At the high frequency end of the spectrum are respiratory fluctuations followed by Mayer waves. These spontaneous variations can be masked by the effects of superimposed physical and mental activity, so they are best studied in a steady-state condition.

Short-term blood pressure variability, of which respiratory fluctuation is the dominant cause, can only be assessed by beat-to-beat monitoring (e.g., intra-arterial recording). Within subjects, both the mean levels and the short-term variabilities of blood pressure and heart rate tend to change in parallel; thus, during sleep there is a decrease not only of blood pressure and heart rate, but also of their variabilities.

Figure 2.4 — Comparison of between- and within-subject changes of short-term blood pressure variability as a function of the average pressure.



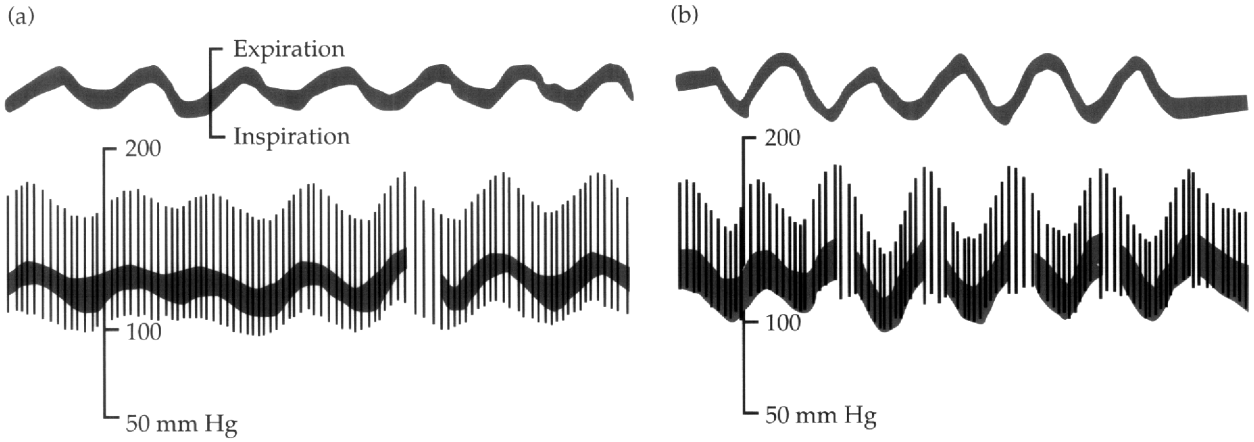
These within-subject changes of variability are shown in Figure 2.4 and are contrasted with between-subject differences in variability.

With increasing age, there is an increase of short-term blood pressure variability and a decrease of heart rate variability.[45] Short-term blood pressure variability is not dependent on the changes of heart rate because it persists after atropinization.[46] Such variability is more pronounced in patients with higher pressures.

2.2.2 Respiration and Blood Pressure Variability

At normal rates of breathing the pressure falls during most of inspiration, but at slower rates, inspiration is associated with a rising pressure (Figure 2.5). Sinus arrhythmia, which is the fluctuation of heart rate associated with respiration, does not contribute to the blood pressure change.[47] The fluctuations of blood pressure are more marked when standing than when supine, as shown in Figure 2.5. Some of the changes of blood pressure can be attributed to the mechanical effects of breathing on venous return and modulation of stroke volume since they persist after ganglionic blockade.

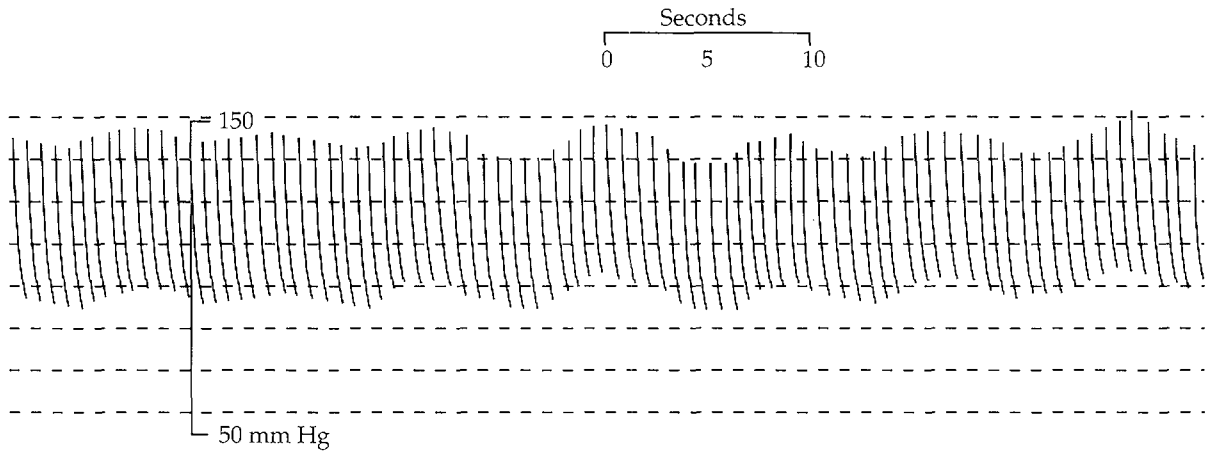
Figure 2.5 — Respiratory fluctuations of blood pressure: (a) while supine; and (b) erect. Upper trace is respiration as measured by a thoracic spirogram; lower trace is blood pressure.



2.2.3 Mayer Waves

There are periodic waves of blood pressure which are slower than the respiratory oscillations — these are usually called Mayer waves — and it has been suggested that they may be mediated via the chemoreceptors. They have a periodicity of 0.07 to 0.12 Hz and can be seen quite clearly during apneic episodes, as shown in Figure 2.6.

Figure 2.6 — Mayer waves occurring during apnea.



2.3 Significance of Blood Pressure Variability

The phenomenon of blood pressure variability is a complex one, and means different things to different people. Following a study of the reproducibility of conventional casual blood pressure measurements, Armitage and Rose wrote: "The clinician should recognize that the patient whose diastolic pressure has fallen 25 mm Hg from the last occasion has not necessarily changed in health at all; or, if he is receiving hypotensive therapy, that there has not necessarily been any response to treatment."[48]

The rationale underlying the use of clinic blood pressure is that it is a surrogate estimate of the true blood pressure. There are several reasons why this estimate might be in error. They include measurement error (e.g., observer bias), error due to the physiologic variability of blood pressure, and error arising from the alerting response or white coat effect. In theory, ambulatory monitoring has the capability of overcoming all of these limitations of clinic measurement for three reasons: the measurements are objective, they are greater in number, and they are taken outside the clinic setting.

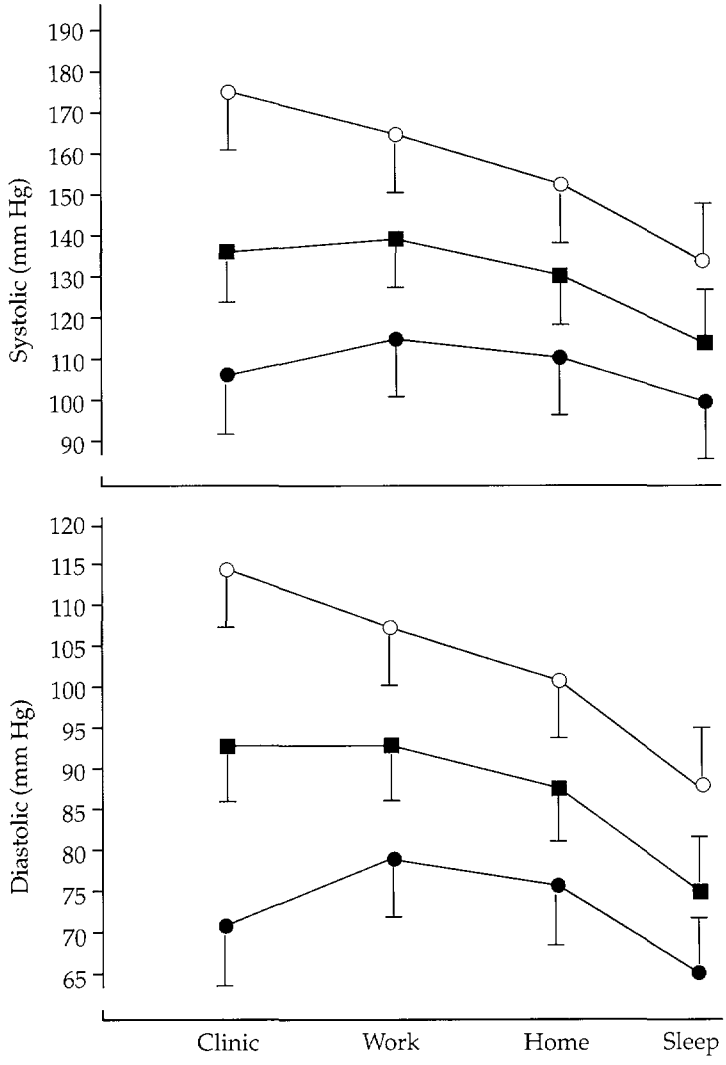
2.3.1 Does Ambulatory Monitoring Improve the Estimate of the True Blood Pressure?

The increased measurement reliability resulting from increasing the number of readings used to estimate the true blood pressure is well recognized, and it has been shown that it is better to increase the number of visits than to take more readings during a single visit.[48] The importance of the number of readings has also been shown in the relationship between blood pressure and target organ damage, where it is well established that ABP correlates more closely with left ventricular mass than clinic pressure (see Section 1.0). This may be attributed to two factors: the greater number of readings obtained with ambulatory monitoring, and the absence of the white coat effect. It is well recognized that clinic blood pressure tends to decrease with repeated

measurement over a series of visits; this trend is not accompanied by any corresponding change of ABP, and may be attributed to regression to the mean or habituation effects.[49] The discrepancy between clinic and ambulatory pressures may be particularly marked in elderly patients with systolic hypertension in whom it has also been shown that ambulatory pressures are more reproducible than clinic pressures.[50]

The discrepancy between clinic and home blood pressure presents the clinician with an important question: which measure of pressure is closest to the "true" level of blood pressure? This question can best be answered by recording blood pressure over 24 hours using ambulatory monitoring. In normal subjects the clinic pressure is similar to or less than the average 24-hour levels, but in hypertensive patients the clinic pressures are higher. As shown in Figure 2.7, which is based on data from normoten-

Figure 2.7 — Comparison of clinic and ambulatory (work, home, and sleep) pressures in three groups of subjects: established hypertensives (○), borderline hypertensives (■), and normotensives (●).



sive and two groups of hypertensive subjects, the disparity between the average clinic pressures of the three groups is much greater than between the corresponding ambulatory pressures.[51]

When the 24-hour period is divided into the three major components — work, home, and sleep, it is apparent that pressures tend to be highest at work, intermediate at home, and lowest during sleep (Figure 2.7). The blood pressure at work is generally similar to the pressure in the clinic, but the correlation between the two is not very close. The correlation between clinic and ambulatory pressures was closer for the normal subjects than for the hypertensives. The traditional argument used to support the use of clinic pressures is that they represent the patient's response to the stresses of everyday life, but this has not been found to be the case (see Section 4.5.5).

2.3.2 What is the Pathological Significance of Blood Pressure Variability?

While it is universally accepted that the level of blood pressure (i.e., the true blood pressure) is a major risk factor for morbidity, it is an open question whether the same is true of blood pressure variability. There has been much recent work on the triggers of acute myocardial infarction, and an increasing awareness that most morbid events show a diurnal rhythm, with increased prevalence during the hours of 6:00 a.m. to noon, when the blood pressure is also at its highest.

Patients whose blood pressure remains elevated during the night may have more extensive target organ damage such as LVH or cerebrovascular damage than those whose pressure shows the normal fall.[52,53] These findings, while suggesting that the diurnal rhythm of blood pressure (or its absence) may have pathological significance, are best explained on the grounds that it is the average level of pressure over 24 hours that is important, and do not necessarily implicate blood pressure variability per se.

A single report has provided preliminary evidence that a blunted nocturnal fall of blood pressure may be an independent risk factor.[54] In a case-control study of patients who had been previously evaluated with ambulatory monitoring, Verdecchia et al. compared 32 patients who suffered morbid events with 49 who had remained healthy. In the men there was no difference in the diurnal rhythm of blood pressure between the cases and controls, but in women the nocturnal fall of pressure was significantly smaller in the cases than the controls. While these results are of great interest, the actual numbers of patients were quite small (only 14 male and 18 female cases), and independent confirmation is needed before they can be translated into clinical action.

There is also one report stating that increased short-term variability of blood pressure may be a risk factor.[55] A group of 73 patients who were evaluated with 24-hour intra-arterial monitoring were followed for an average of seven years, at which time the severity of target organ damage was assessed with echocardiography. The variability of blood pressure over 24 hours was an independent predictor of the degree of target organ damage. Although these results must also be considered as preliminary, the estimate of blood pressure variability from continuous intra-arterial measurement is more precise than from intermittent noninvasive recording.

3.0 AMBULATORY BLOOD PRESSURE IN NORMAL POPULATIONS

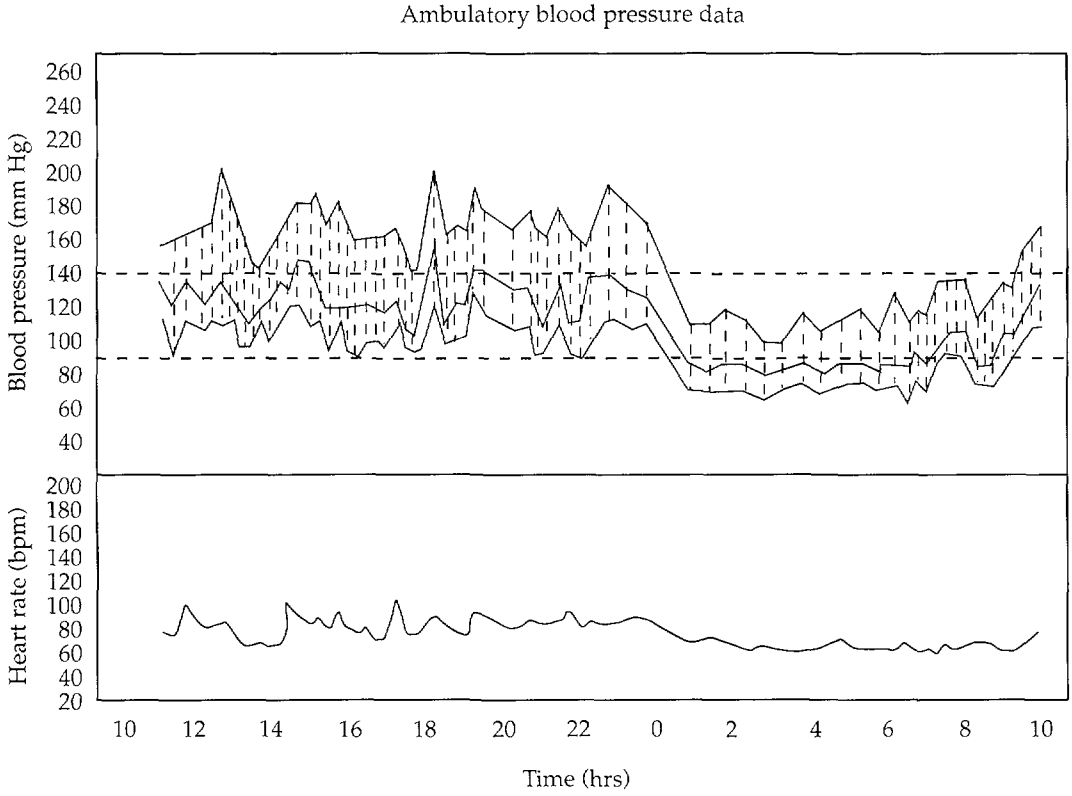
In order to interpret ABP recordings made in patients with hypertension and other clinical disorders, it is necessary to understand the normal levels and changes occurring during daily life. These are reviewed in this section.

3.1 Diurnal Rhythm of Blood Pressure

3.1.1 Two Models that Explain the Diurnal Rhythm of Blood Pressure

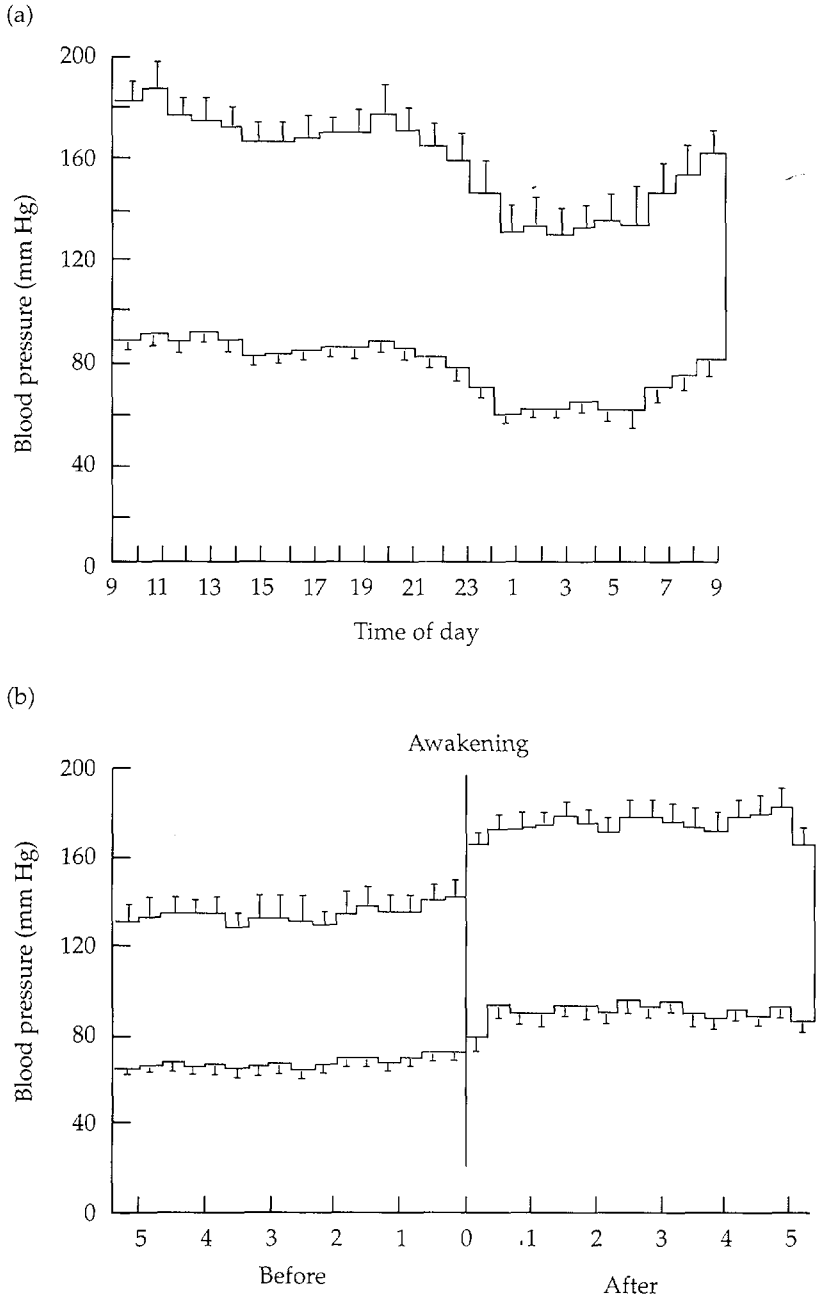
Recordings made over 24 hours in ambulatory subjects show that blood pressure tends to be highest in the morning, with a gradual decrease over the course of the day, and lowest during the night (Figure 3.1).[56,57] Two explanations have been proposed to describe this phenomenon. The first is that there is an intrinsic circadian rhythm of blood pressure analogous to the circadian pattern of cortisol or body temperature.[58] It has also been proposed that there is a gradual increase of blood pressure during the early morning hours (3:00 a.m. to 6:00 a.m.) before the time of waking.[56]

Figure 3.1 — The diurnal rhythm of blood pressure, recorded in a hypertensive subject with a SpaceLabs Medical 90207 ambulatory monitor.



The second explanation is that the rhythm is determined by the levels of rest and activity, including sleep and wakefulness. According to this view, which is supported by the bulk of the evidence described below, the apparently sinusoidal pattern of blood pressure is largely an artifact attributable to the averaging of records from individuals who wake at different times. When the recordings are synchronized to the time of waking rather than the time of day, the early morning rise of pressure is much less pronounced.[59] Instead, blood pressure remains relatively stable during the hour

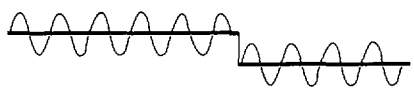
Figure 3.2 — Diurnal rhythm of blood pressure: (a) pooled data for 14 hypertensive subjects plotted according to clock time; and (b) same data plotted according to time of waking.



before waking, but rises abruptly at the moment of waking (Figure 3.2). This pattern is consistent with the changes described in studies where electroencephalogram (EEG) was recorded as well as blood pressure.[60]

The question whether there is an endogenous circadian rhythm of blood pressure, or whether the changes can be accounted for by variations in activity, is an important one. It can best be answered by removing the influence of external stimuli, so that if the rhythm persists it can be attributed to endogenous factors. Thus, a study of patients in an orthopedic ward who were immobilized by plaster casts found that the blood pressure showed no evidence of any sinusoidal change, being relatively constant during the day and decreasing during sleep. There were, in effect, two levels of pressure — one corresponding to waking and the other to sleeping.[61] Subjects who take an afternoon nap show a decline of blood pressure that is similar to the nocturnal decrease, suggesting that it is the effect of sleep itself rather than the time of day which is responsible.[62] In addition, analysis of individual diurnal blood pressure profiles has shown that activity is a better predictor of the changes than time of day.[57] These two models of the diurnal variations of blood pressure are summarized in Figure 3.3.[63] The set point model (Figure 3.3a) assumes that blood pressure fluctuates around two set points, one corresponding to wakefulness, the other to sleep. The underlining is extrinsic, since the major determinants are activity and arousal. The oscillator model (Figure 3.3b) is regulated by an internal oscillator or biological clock.

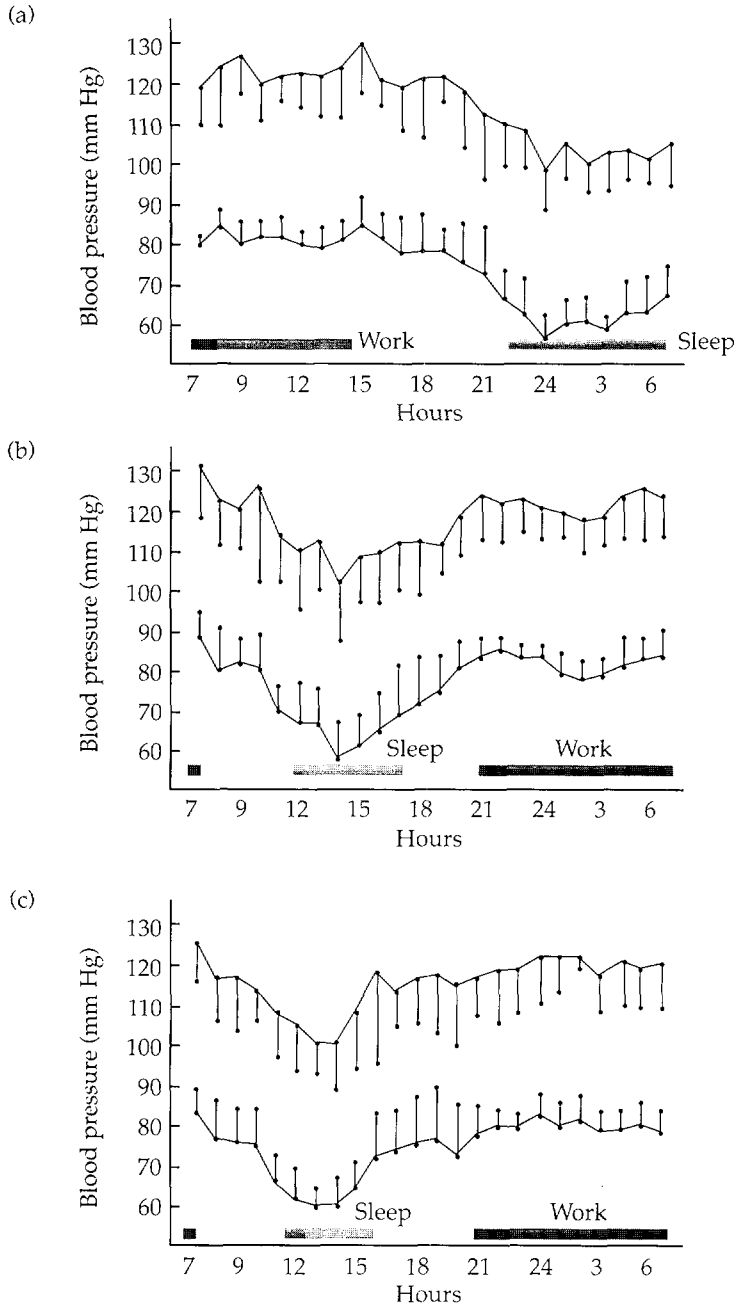
Figure 3.3 — Two models to describe the diurnal rhythm of blood pressure: (a) set point; and (b) oscillator.

	(a) Set point 	(b) Oscillator 
Underlying mechanism	Extrinsic	Intrinsic
Major determinants	Activity/arousal	Time of day
Adjust to phase shift	Immediate	Delayed
Pattern	Asymmetrical	Symmetrical
Fits cosine model	No	Yes

3.1.2 Diurnal Rhythms in Shift Workers

Studies of shift workers have shown a close link between activity and blood pressure. When individuals, such as nurses, change from working a day shift to a night shift, their blood pressure rhythm follows closely the cycle of rest and activity, as shown in Figure 3.4.[64]

Figure 3.4 — Diurnal rhythms of blood pressure on three different work shifts: (a) daytime shift; (b) first day of night shift; and (c) last day of night shift.



3.1.3 Blood Pressure Changes Associated with Sleep and Wakefulness

Sleep is an active process regulated by centers in the brainstem and composed of distinct cycles that recur regularly throughout the course of the night. Two basic vari-

eties are recognized — nondreaming, or slow-wave sleep and dreaming, or rapid eye movement (REM) sleep. The deepest stages of slow-wave sleep (stages 3 and 4) occur in the first two hours of sleep; periods of REM sleep occur in 90-minute cycles, with episodes lasting longer during the latter part of the night.

Blood pressure changes are closely linked to the level of arousal. During the first hour of sleep there is normally a progressive fall in blood pressure, which usually shows its maximal decrease of 15 to 20% two hours after sleep onset, as shown in Figure 3.5.[60,65] This coincides with the deepest stages of slow-wave sleep (stages 3 and 4). During REM sleep, the blood pressure is about the same as in stage 2 (approximately 10% less than during wakefulness) but is much more variable, with fluctuations of as much as 30 mm Hg over a few minutes.[66]

Blood pressure rises immediately on waking, but an even bigger increase occurs at the time of arising as shown in Figure 3.6.[67]

The use of noninvasive ABP recorders to monitor blood pressure changes during sleep has been reported to provoke some degree of arousal, but without having any significant effect on blood pressure itself.[68,69]

3.2 Effects of Physical and Mental Activity on Blood Pressure Variability

If the effects of environmental stimuli and changes in physical activity are minimized, the profile of blood pressure during the day becomes relatively flat, with a small decrease occurring during sleep.[61] It has also been shown that diurnal blood pressure changes are less pronounced in hospitalized patients than in patients studied in their natural environment.[70] Both the average level of blood pressure and its variability are reduced during periods of bed rest as compared to periods of physical activity.[71]

It is possible to monitor physical activity by an electronic device known as an actigraph, worn on the wrist or waist and which registers body movement in one minute epochs over periods of 24 hours. This shows a close parallelism between changes of physical activity and blood pressure (Figure 3.7).[72]

Figure 3.5 — Typical blood pressure changes during sleep in a normal subject. Upper trace shows sleep stages. Blood pressure is plotted every 60 seconds, and every 30 seconds during REM sleep, to show increased variability.

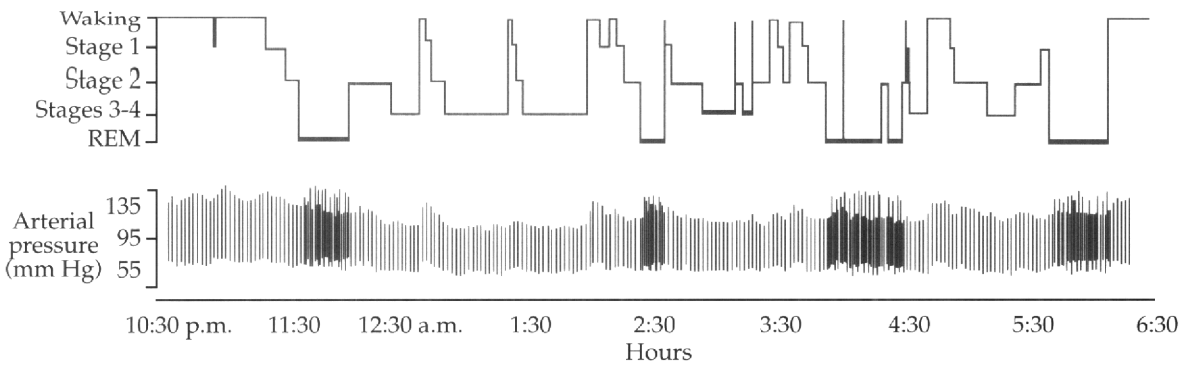


Figure 3.6 — Levels of systolic pressure, diastolic pressure, and heart rate in normotensive subjects monitored for 1 hour before waking to 1 hour after waking. Subjects either got up immediately on waking, or remained supine for 1 hour.

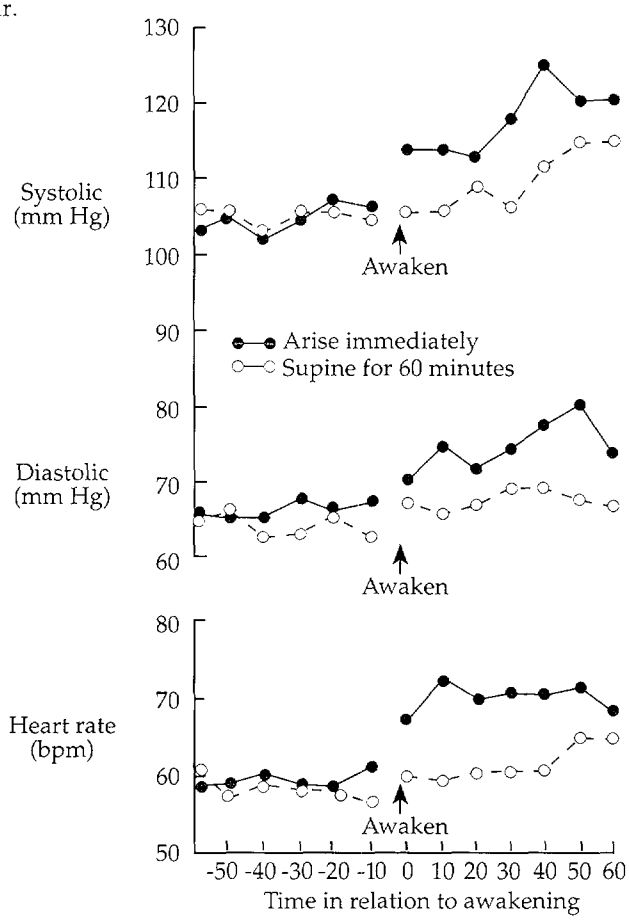
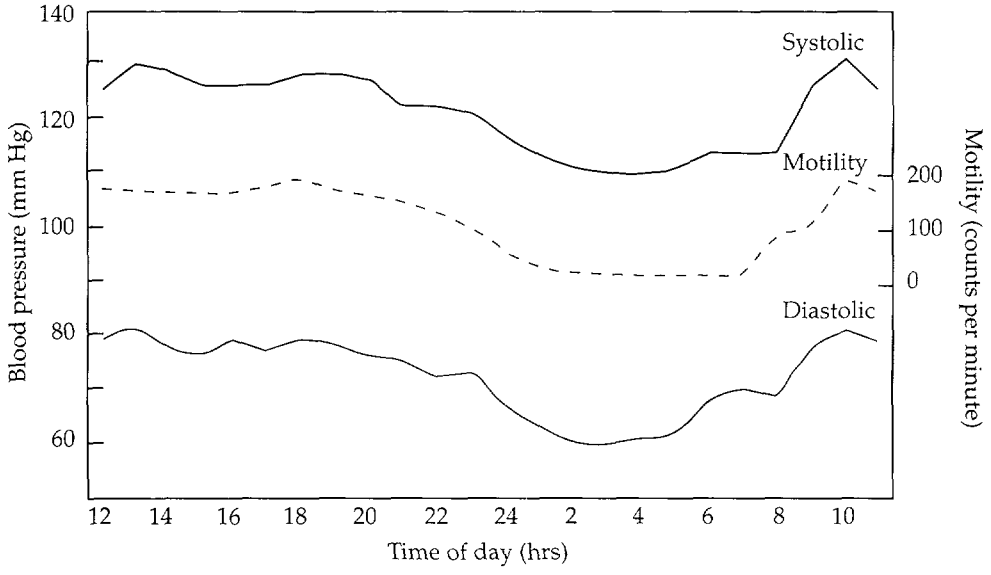


Figure 3.7 — Diurnal profile of systolic pressure, diastolic pressure, and motility measured with an actigraph.



Some of the more relevant activities influencing the changes of blood pressure and other variables that might be detected by ambulatory monitoring are briefly reviewed below; they are divided into physical and mental activities, although obviously there is considerable overlap.

3.2.1 Changing Posture

Posture is an important source of blood pressure variability, particularly in ambulatory monitoring studies. In an individual, changing from the supine to the upright position causes an increase of diastolic pressure with little or no change of systolic pressure. In ambulatory monitoring studies, changes of posture account for a major portion of overall blood pressure variance.[73] This can largely be explained by the effects of the activities associated with different postures rather than the postures themselves; as shown in Table 3.1, the changes in blood pressure occurring simply as the result of changing posture can be rather modest.

Table 3.1 - Typical Effects of Postural Change on Blood Pressure

Posture	Blood Pressure (mm Hg)
Supine	137/76
Sitting	139/84
Standing	133/86

These readings were obtained during a validation study of an ABP monitor.

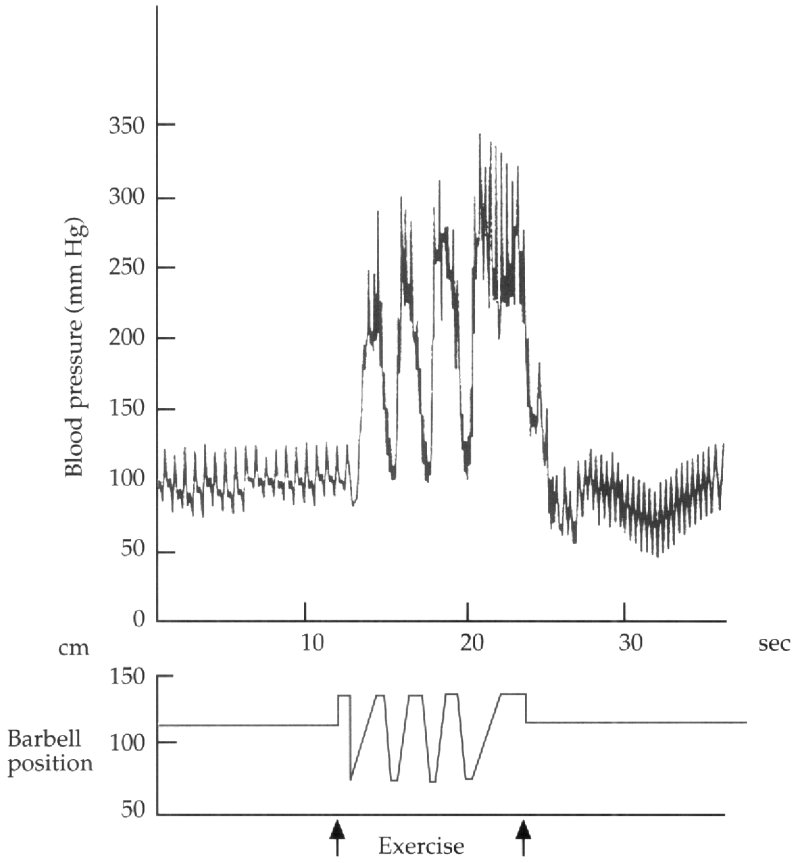
3.2.2 Dynamic Exercise

Dynamic exercise raises systolic pressure and heart rate, with little effect on diastolic pressure. In normotensive subjects, systolic pressure during intense exercise may reach 200 mm Hg or more. Noninvasive ABP recorders cannot reliably measure these changes, however, because of movement artifact.[74] Following a prolonged bout of dynamic exercise there may be a period of postexercise hypotension lasting several hours.[75] In normotensives this reduction may be as much as 10 mm Hg in systolic pressure and 5 mm Hg in diastolic pressure. Larger changes are seen in hypertensives.

3.2.3 Static (Isometric) Exercise

Static exercise, such as occurs during weight-lifting, produces a very different blood pressure response with a marked increase of both systolic and diastolic pressures. The extent of this increase is a function of the intensity of contraction rather than of the bulk of muscle being used — at 50% of maximal voluntary contraction mean arterial pressure may increase by 40 mm Hg within one minute.[76] Lifting barbells can produce huge increases of intra-arterial pressure, with levels as high as 345/245 mm Hg having been recorded, as shown in Figure 3.8.[77]

Figure 3.8 — Intra-arterial blood pressure changes while lifting barbells. Four repetitions were performed.



3.2.4 Sexual Intercourse

Sexual intercourse is another form of exercise that can produce a dramatic transient rise of pressure — ranging from 25 to l20 mm Hg in systolic pressure, and 24 to 48 mm Hg in diastolic pressure.[78] These changes are reversed within a few minutes after orgasm.

3.2.5 Micturition and Defecation

Micturition and defecation produce transient changes that resemble a Valsalva maneuver, with a brief rise of pressure followed by a precipitous fall, and then a marked rise corresponding to the overshoot phase of the Valsalva.[79]

3.2.6 Eating and Drinking

In younger subjects there is an increase of heart rate, a decrease of diastolic pressure, and little change of systolic pressure three hours after a meal.[80] In older subjects there may be a pronounced fall of both systolic and diastolic pressure after eating.[81]

3.2.7 Smoking

Smoking a cigarette raises both heart rate and blood pressure, the latter by as much as 5 to 10 mm Hg.[82] The effect on blood pressure is seen within a few minutes and lasts about 15 minutes. In hypertensive subjects, particularly those over the age of 50, smoking raises the daytime ABP.[83]

3.2.8 Alcohol

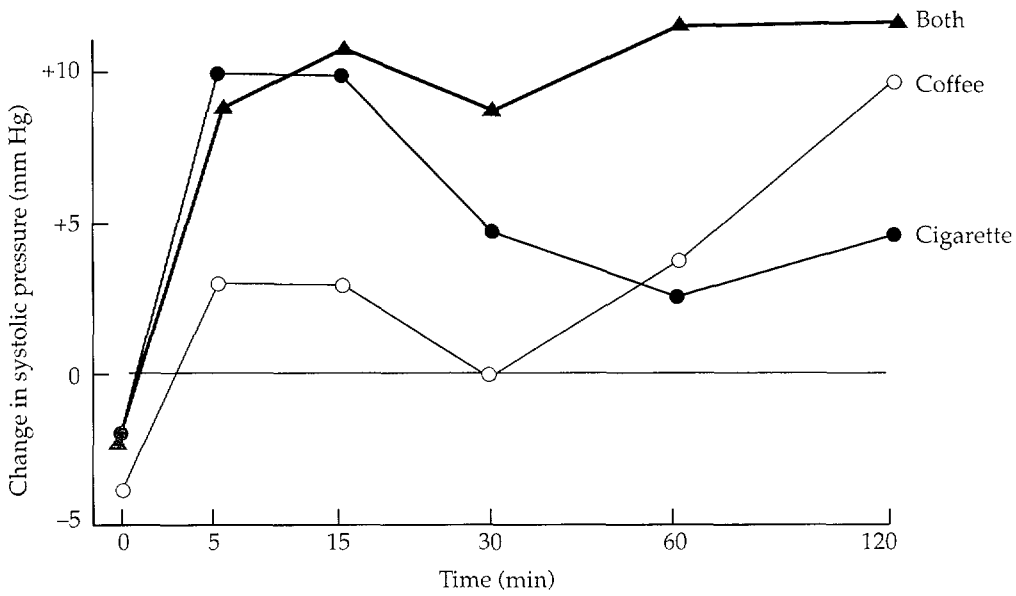
Drinking alcohol may increase heart rate, with small but variable effects on blood pressure in normal subjects, ranging from no significant change to an increase of 5/7 mm Hg at one hour after ingestion of one to three drinks.[84,85] It has been reported that four days of drinking alcohol does not affect the 24-hour blood pressure level.[86] However, it is also well recognized that prolonged alcohol consumption contributes to the development of hypertension.[87]

3.2.9 Caffeine

Ingesting caffeine increases blood pressure but not heart rate.[88] The increase of blood pressure begins within 15 minutes of drinking coffee, is maximal in about 1 hour, and may last for as long as three hours. Typical increases are between 5/9 mm Hg and 14/10 mm Hg.[89] Drinking decaffeinated coffee produces little or no change.[88] Caffeine also has an additive effect on the blood pressure response to mental stress — higher absolute levels of pressure are achieved after caffeine, but the rise of pressure during the stressor is not affected. Coffee drinking can also raise the ABP recorded at work.[90]

Coffee and cigarettes are often taken together and they may have an interactive effect.[91] As shown in Figure 3.9, smoking a cigarette elevated blood pressure for 15

Figure 3.9 — Effects of smoking a cigarette and drinking coffee, alone and together, on systolic blood pressure.



minutes, whereas drinking coffee had no effect for one hour, when there was a significant increase. When the cigarette and coffee were taken together, however, there was a significant increase of pressure of about 10 mm Hg which was seen within 5 minutes, and was still present two hours later.

3.2.10 Talking

Talking is potent pressor stimulus that has both physical and psychological components.[92,93] Reading aloud produces an immediate increase of both systolic and diastolic pressure (by about 10/7 mm Hg in normotensive individuals) and of heart rate, with an immediate return to baseline levels once silence is resumed.[92] Reading silently however, does not affect pressure. Speaking fast produces a bigger increase than speaking slowly.[93] The role of psychological factors is shown by the finding that talking in front of a group produces a larger increase than reading aloud while alone.[92]

3.2.11 Mental Activity and Emotion

There is some correlation between self-rated mental stress or arousal and blood pressure during noninvasive ambulatory monitoring. Blood pressure tends to be higher when people are at work than when they are at home, which may be attributed to mental as well as physical factors.[57,94,95]

Mood has also been reported to be a potent determinant of blood pressure during ambulatory monitoring. Self-reported levels of anger, anxiety, and happiness are correlated with blood pressure — systolic pressure decreased as the intensity of happiness increased, and diastolic pressure increased with the intensity of anxiety.[96]

3.3 Seasonal Variations of Blood Pressure

Blood pressure tends to be about 5 mm Hg higher in winter than in summer. The effect appears to be a direct consequence of changes in environmental temperature, and is more marked in older than younger subjects, although it has also been observed in children.[97,98]

3.4 What is a Normal Ambulatory Blood Pressure?

Physicians who use ambulatory recordings for the diagnosis or evaluation of patients with mild hypertension are faced with the problem that there is no reason why any cutoff point based on clinic measurement of blood pressure should also be valid for ambulatory measurements. Therefore, some estimate of the range of ABP in normotensive individuals is needed.

For ambulatory monitoring to become clinically useful, there is a need to develop some sort of criteria of normality, notwithstanding the problems already discussed with the definition of a normal clinic pressure. The problem here is how the normal range should be established. Some examples of measures that have been proposed are listed below. The first three are based on estimates of the upper limit of ABP in a normotensive population. While this represents the traditional method for defining the

normal range of any biological variable, in this particular case it requires the prior exclusion of hypertensive patients. This, of course, has to be done by using criteria based on conventional clinic measurements, so that the ABP limits will be largely determined by these selection criteria. Some published upper limits are shown in Table 3.2. (See also Table 8.1 in Section 8.0 for practical guidelines regarding normal ranges.)

Table 3.2 – Proposed Upper Limits of Normal Daytime Ambulatory Blood Pressure

Criterion	Author	Reference	N	Limits
90th percentile of "normal" population	Pickering	99	38	134/90
95th percentile of "normal" population	Staessen	100	3476	146/91
	Palatini	102	60	133/87
	O'Brien	103	815	148/94
ABP equivalent to clinic BP of 140/90 mm Hg	Palatini	102	522	126/83
	Baumgart	104	1039	135/84
Threshold for increased prevalence of LVH	Verdecchia	105	191	136/90
	Devereux	106		139/86

3.4.1 Criteria Used to Define the Upper Limit of Normal

3.4.1.1 90th Percentile of a Normal Population

The 90th percentile of a normal population was used in one study, with a limit of 134/90 mm Hg.[99]

3.4.1.2 95th Percentile of a Normal Population

A meta-analysis of 23 studies of 3,476 normotensive individuals gave an upper limit of normal of 146/91 mm Hg for daytime and 139/87 mm Hg for 24-hour ABP.[100] A second analysis, which pooled much of the same data (4,577 normotensive subjects from 24 research groups), found a 95th percentile of 133 mm Hg for systolic 24-hour pressure and 82 mm Hg for diastolic pressure.[101]

3.4.1.3 Blood Pressure Load of a Normal Population

Blood pressure load of a normal population is defined as the percentage of readings above a certain threshold level — usually 140/90 mm Hg.[105,106] Two variations of this

approach have been either to use the same threshold level for the entire 24 hours, for which it has been suggested that the upper limit of normal for the diastolic load should be 15%, or to use 140/90 mm Hg during the day and 120/80 mm Hg during the night.[107,108] The theoretical limitation of this concept is that it presupposes a threshold level of blood pressure, whereas, in effect, we know that the relation between blood pressure and risk is curvilinear. An alternative version is to express the load as the area under the curve above a threshold level.[109] This is theoretically better, but still arbitrary.

Suggested ranges of normal blood pressure loads are shown in Table 8.1 in Section 8.0.[99-106]

3.4.1.4 Ambulatory Pressure Equivalent to a Clinic Pressure of 140/90 mm Hg

The rationale of this procedure is that we can at the present time only relate cardiovascular risk to clinic pressure, because this was used in all the epidemiological and actuarial studies relating blood pressure to morbidity. Baumgart et al. derived a linear regression equation relating clinic and ABP from a large population of patients with varying degrees of hypertension in order to determine what level of daytime ABP is equivalent to a generally accepted cutoff point for clinic pressure (such as 140/90 mm Hg).[104] For their data this was 135/85 mm Hg; for a clinic pressure of 160/95 mm Hg the corresponding value would be 146/87 mm Hg. Similar regression equations have been published previously by Perloff et al. which give approximately the same ABP for each clinic pressure (for clinic pressures of 140/90 mm Hg and 160/95 mm Hg the corresponding ambulatory pressures would be 133/84 mm Hg and 145/87 mm Hg).[110,111]

3.4.1.5 Ambulatory Pressure Related to Target Organ Damage

Since the purpose of defining an upper limit of normal ABP is to define a level of pressure associated with a low level of risk, a more logical approach is to relate different levels of ABP to the prevalence of target organ damage, as measured by echocardiography for example. This approach has been successfully used by Verdecchia et al. who found that there was a marked increase in the prevalence of LVH above an average daytime ABP of 136/87 mm Hg in men, and 131/86 mm Hg in women.[105]

3.4.2 Normal Ambulatory Blood Pressure in Special Populations

When considering the definition of a normal ABP it is important to recognize that a number of demographic variables may influence both the average level of blood pressure and its variations. Of these, the most important are age and gender, although once again the available data are relatively scarce. The factors known to influence ABP in healthy individuals are discussed below.

3.4.2.1 Effects of Age

The normal diurnal pattern of blood pressure consists of a decrease of 10 to 20% during the hours of sleep, which is seen in both normotensive and hypertensive individuals.[112] This pattern appears to be altered in many elderly individuals (defined as those older than 65 years of age), although the published data are somewhat inconsistent. Some studies having reported a loss of the nocturnal fall in the elderly, and others no difference from younger subjects. In elderly patients with isolated systolic hypertension, the nocturnal fall of both systolic and diastolic pressure has been reported to be greater than in age-matched normotensives or diastolic hypertensives, without any difference in the changes of heart rate.[113]

One explanation for the apparent loss of the diurnal rhythm in some elderly patients is that their sleep pattern is likely to become fragmented. None of the reported ambulatory studies have measured the duration or depth of sleep, and there is no good reason to suppose that the blood pressure changes with sleep are altered in the elderly. Another is that there are many clinical disorders which are associated with a loss of the diurnal rhythm, which are more likely to be present in older than in younger individuals. Examples are chronic renal failure and autonomic neuropathy, which are described in Section 4.0.

The normal range of ABP in the elderly has not been clearly established, but from published data should be at least 5 mm Hg higher than in younger subjects.[103]

3.4.2.2 Effects of Gender

Several studies have shown that ABP is lower in premenopausal women than in men.[103] Adolescent boys have been reported to have slightly higher systolic ambulatory pressures (by 4 mm Hg) than girls, but similar diastolic pressures.[114] Ambulatory blood pressure in children is discussed in Section 5.0.

3.4.2.3 Effects of Race

A diminished nocturnal fall of blood pressure has been reported for adolescent and adult blacks of both sexes in studies performed in the United States using noninvasive monitors.[114,115] However, other studies performed in other countries and in the U.S. have failed to find a difference in the diurnal patterns of black and white adults.[116,117] These different findings are probably due to environmental and demographic factors rather than to genetic factors.

4.0 AMBULATORY MONITORING TO DIAGNOSE DISEASE

By far the most important clinical application of ambulatory monitoring is the evaluation of patients with known or suspected high blood pressure. Despite the fact that all the epidemiological studies describing its risks, and all the interventional studies describing the benefits of its treatment were performed with conventional clinic measurements, it is well recognized that such readings may give misleading information in many patients. The general tendency is for clinic pressures to overestimate the true

blood pressure (leading to the diagnosis of white coat hypertension in extreme cases), although there is a smaller number of patients in whom clinic pressure underestimates true pressure.

In addition to providing a better estimate of the average, or true, blood pressure, ambulatory monitoring may reveal changes in the variations of blood pressure over 24 hours which would not be detected by more conventional means of measuring blood pressure. Two important examples are alterations in the pattern of the diurnal rhythm of blood pressure and increases in short-term blood pressure variability. These advantages of ambulatory monitoring provide the primary rationale for its clinical use. Information provided by ambulatory monitoring includes:

- The average blood pressure level
- Changes in diurnal rhythm of blood pressure
- Changes in short-term blood pressure variability.

4.1 Rationale for the Clinical Use of Ambulatory Monitoring

4.1.1 Measurement of True Blood Pressure

More than 50 years ago, Ayman and Goldshine observed that in 34 cases of hypertension, blood pressures recorded by the patients at home were consistently lower than pressures recorded by the physicians at their offices — in some cases by as much as 70/36 mm Hg.[118] This discrepancy between clinic and home blood pressures has been consistently confirmed and is roughly proportional to the height of the clinic pressure (Figure 4.1) being virtually non-existent in normotensive individuals.[119] Since there is no a priori reason why hypertensives and normotensives should respond differently in these situations, the differences may represent an example of the white coat effect. Hypertension is conventionally defined on the basis of clinic pressures, so that any individual whose blood pressure tends to increase in the presence of a clinician will be selected out of the population and labelled as being hypertensive.

In hypertensive patients clinic blood pressure tends to decrease with repeated visits, even in the absence of any intervention. In some cases, it may take as many as six visits before a plateau level of pressure is reached.[120] The most plausible explanation for this phenomenon is that it represents a habituation of the pressor response that occurs at the time of a clinic visit; regression to the mean may also contribute. Thus, the difference between clinic and home readings also tends to diminish.[121]

A comparison of clinic and daytime ABP for a mixture of 573 normotensive and mildly hypertensive subjects is shown in Figure 4.2.[122] The subjects can be divided into four groups: those who are hypertensive both in the clinic and during ambulatory monitoring (the sustained hypertensives); those who are normotensive in both settings (the true normotensives); those who are hypertensive in the clinic and normotensive during ambulatory monitoring (the white coat hypertensives); and those who are normotensive in the clinic and hypertensive during ambulatory monitoring (a group for whom there is no recognized nomenclature, but who may be regarded as pseudonormotensives).

An important point to note is that the clinic pressure tends to exceed the ABP in the overwhelming majority of hypertensive subjects, be they sustained or white coat

Figure 4.1 — Comparison of the average levels of clinic and home (self-monitored) systolic blood pressure. Data from 14 published studies.

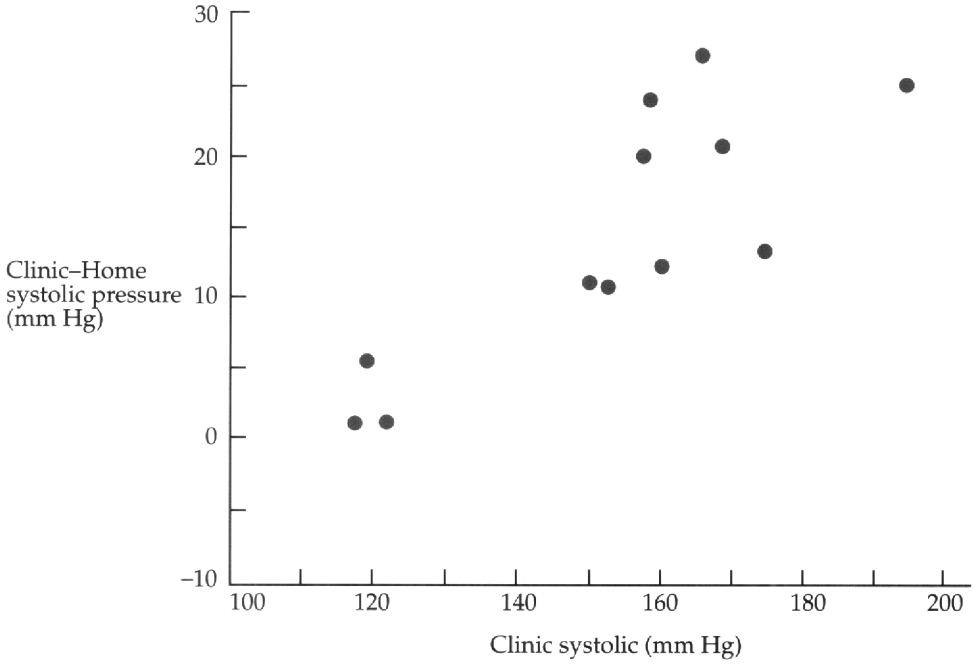
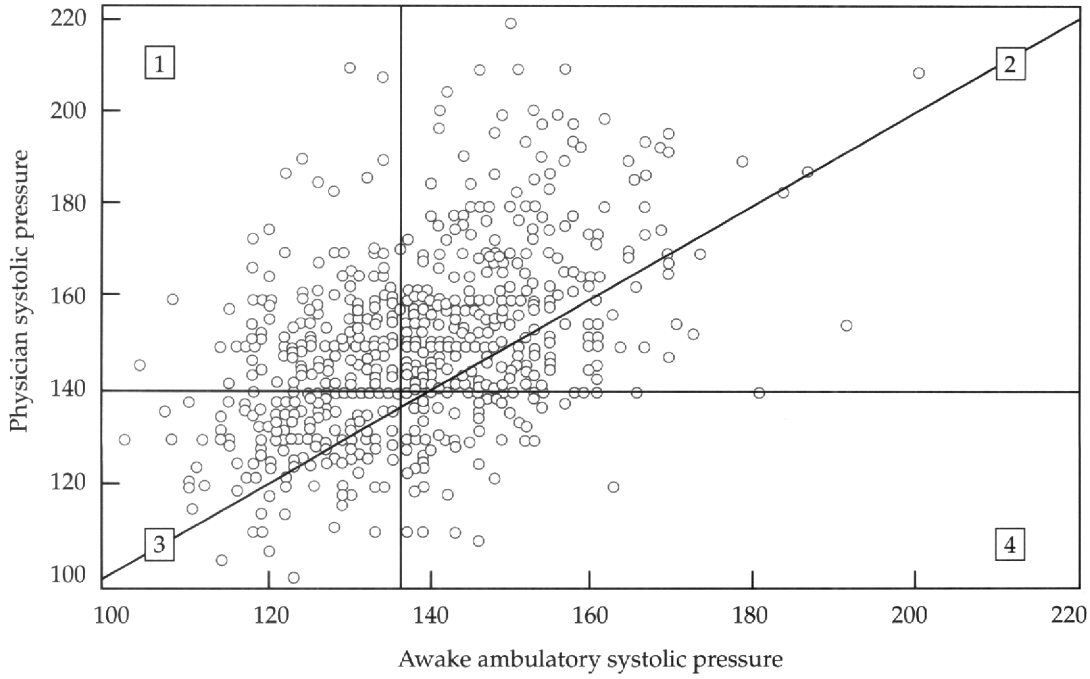


Figure 4.2 — Plot of clinic (physician) and daytime (awake) ambulatory pressure in 573 patients. Diagonal line is line of identity. Four quadrants are: 1. white coat hypertensives; 2. true hypertensives; 3. true normotensives; and 4. pseudonormotensives.

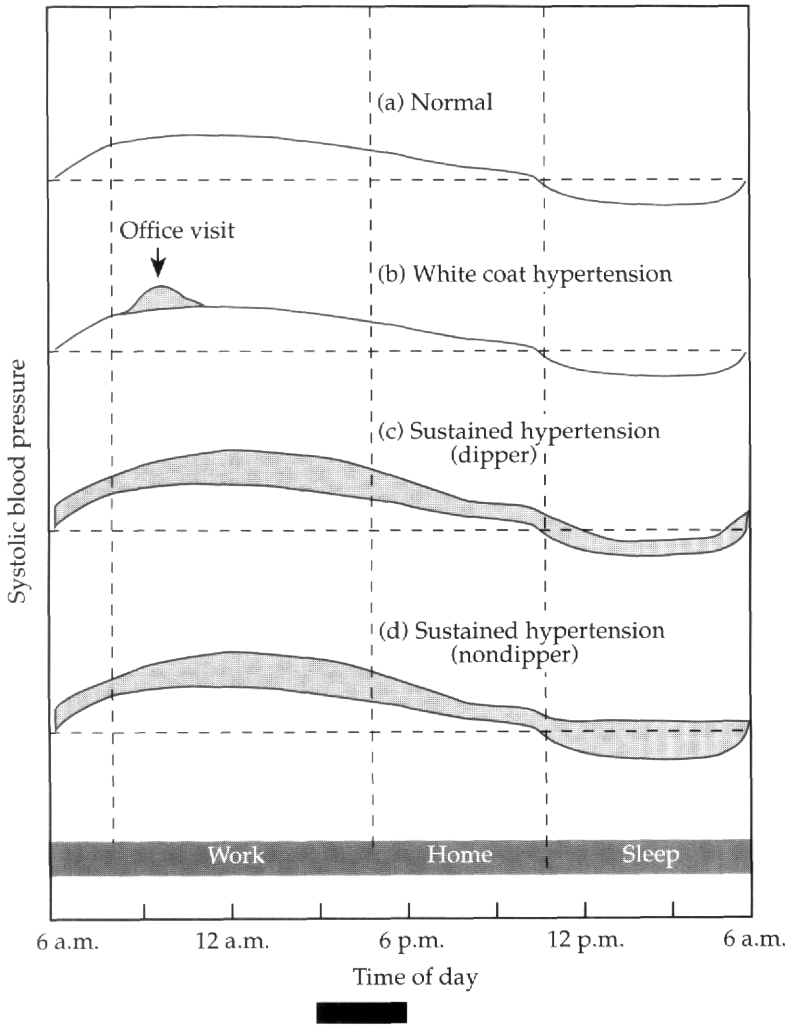


hypertensives. The distinction between the two groups of hypertensives is thus quite arbitrary and there is no natural dividing line that can be discerned from the blood pressure levels.

4.1.2 Estimation of Changes in the Diurnal Rhythm of Blood Pressure: Dippers and Nondippers

As shown schematically in Figure 4.3, ambulatory monitoring may reveal a spectrum of diurnal patterns of blood pressure in patients with elevated clinic readings. First, some patients will have white coat hypertension (Figure 4.3b) with normal ambulatory readings. Patients with persistently elevated ambulatory pressures, or sustained hypertension, may be subdivided in those who show a normal nocturnal fall of pres-

Figure 4.3 — Different diurnal rhythm patterns which may be detected by ambulatory monitoring in patients who have high clinic readings. The grey areas show the degree of elevation above normal.



sure, the dippers (Figure 4.3c), and those whose pressure remains high, the nondippers (Figure 4.3d).[123,124]

There is no universal agreement as to how dippers and nondippers should be defined. A nocturnal fall of less than 10% may be a useful cutoff point. Nighttime has often been defined by some arbitrary time period (e.g., 10:00 p.m. to 6:00 a.m.), but is more accurately defined by recorded sleep time.

This distinction between dippers and nondippers may be of interest for several reasons; first, it may be helpful in understanding the regulation of blood pressure during sleep and wakefulness; second, the findings of an absent nocturnal blood pressure fall may be of diagnostic value; and third, it may have prognostic value as well. A problem that is sometimes overlooked is that the observation of an absent nocturnal fall of blood pressure may simply be due to the fact that the patient did not sleep, or, if noninvasive blood pressure monitoring was used, was aroused by the inflation of the blood pressure cuff. However, in the conditions in which the diurnal rhythm of blood pressure is abnormal there is usually a decrease of heart rate during the night, which should help distinguish the nondippers from the nonsleepers. These conditions include:

- Essential hypertension (nondippers)
- Malignant hypertension
- Chronic renal disease
- Pheochromocytoma
- Pre-eclamptic toxemia
- Cushing's syndrome
- Orthostatic hypotension
- Diabetes with autonomic neuropathy
- Congestive heart failure
- Cardiac transplantation
- Hyperthyroidism.

On the grounds that it is the true blood pressure which determines cardiovascular damage, it is reasonable to hypothesize that patients whose blood pressure remains elevated at night (nondippers) will be at higher risk than those whose pressure falls (dippers). In support of this, there is some evidence that there is a higher prevalence of target organ damage, either LVH or disease of major arteries, in nondippers than in dippers.[125,126] Albuminuria is also commonly seen in nondippers.[127]

It is also well established that there is a diurnal rhythm of the incidence of acute cardiovascular events. This has been described for myocardial infarction, angina, sudden cardiac death, cerebral hemorrhage, and cerebral thrombosis.[128] While all of these show a diurnal trend in parallel with the normal diurnal blood pressure rhythm (with a peak between 6 a.m. and noon), it cannot be stated that the blood pressure is the prime culprit since other indices of sympathetic nervous activity (e.g., heart rate and platelet stickiness) show similar diurnal changes. Nevertheless, it is quite possible that the risks of such acute events are greater in patients who show bigger diurnal swings of blood pressure.

4.1.3 Measurement of Changes in Short-Term Blood Pressure Variability

Individual patients are commonly given the diagnosis of labile hypertension. This term was once used to describe patients with borderline hypertension whose pressure was sometimes above and sometimes below an arbitrary dividing line, while those with more severe hypertension, whose pressure was always above this point, were regarded as having fixed hypertension. It is now quite clear that hypertension does not go through a transient phase of increased variability, and that the trend is for variability to continue to increase along with the patient's age and blood pressure.

Nevertheless, there are patients whose blood pressure does show an increased variability. Some of these will merely represent the upper end of the distribution curve of blood pressure variability. Others, less commonly, may have a discrete lesion of their central or peripheral nervous system which impairs the normal blood pressure homeostasis. The clinical conditions associated with increased blood pressure variability are:

- Aging
- Severe hypertension
- Pheochromocytoma
- Autonomic neuropathies
- Baroreceptor denervation
- High spinal cord lesions.

One example of a central nervous system lesion which increases blood pressure variability is denervation of the baroreceptors. This may result from bilateral carotid artery surgery or, possibly, from severe bilateral carotid atherosclerosis; the lesion is on the afferent side of the reflex arc and the efferent sympathetic nerves are intact. Blood pressure variability is increased with episodes of both hypo- and hypertension.[129]

In patients with high spinal cord lesions which result in tetraplegia or paraplegia, the connections between the central and peripheral components of the sympathetic nervous system are interrupted. This results in a disinhibition of visceral cardiovascular reflexes, so that situations such as bladder distension or muscle spasm produce paroxysmal hypertension. A unique feature of this condition is that these episodes are associated with a reflex bradycardia, mediated via the vagus nerve.[130]

4.2 Clinical Indications for Ambulatory Monitoring

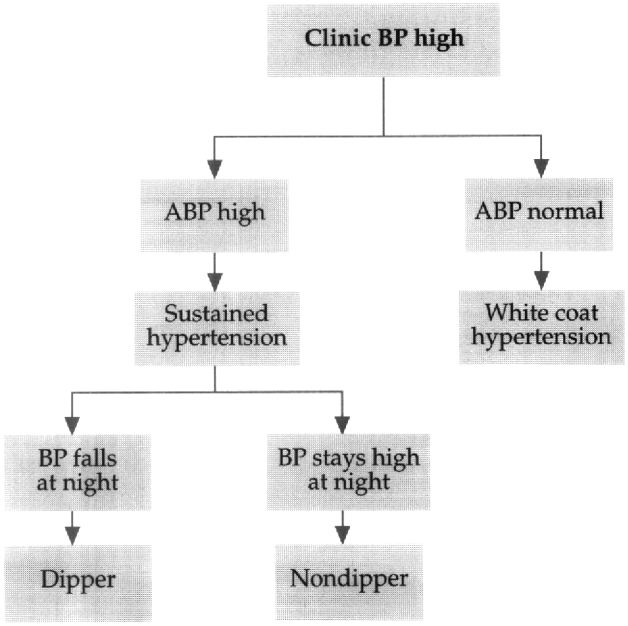
While some would argue that, at the present time, there are no clearly defined clinical indications for ambulatory monitoring, there are a number of situations where a better knowledge of what is happening to a patient's blood pressure over 24 hours might lead to different therapeutic decisions. The major clinical indications for ambulatory blood pressure monitoring are:

- Evaluation of newly diagnosed hypertensive patients without target organ damage
- Disparity between clinic and home blood pressures
- Evaluation of resistant hypertension
- Intermittent symptoms possibly related to blood pressure
- Episodic hypertension
- Orthostatic hypotension/autonomic neuropathy.

The most common general indication is the evaluation of patients who are hypertensive in the clinic. Here, the major finding of interest is whether or not the average ABP is raised (Figure 4.4). This will distinguish between patients with sustained hypertension and those with white coat hypertension. For those with sustained hypertension, the next consideration is whether the blood pressure falls or remains elevated during the night (i.e., whether the patient is a dipper or a nondipper). Being classified as a nondipper may simply mean that the patient did not sleep well during the recording session, but may also be characteristic of the clinical conditions listed in Section 4.1.2.

Ambulatory monitoring may also be of value in patients who are normotensive during routine clinical evaluation, but who are suspected of having episodes of hyper- or hypotension. Some specific situations in which ambulatory monitoring may be clinically indicated are discussed below.

Figure 4.4 — Classification of patients who are hypertensive in the clinic according to the level and pattern of ambulatory blood pressure.



4.2.1 Evaluation of Newly Diagnosed Hypertensives without Target Organ Damage

In many patients, particularly those with mild hypertension, the only detectable abnormality is an elevated blood pressure, so that the therapeutic decisions that are finally reached will depend on how the blood pressure is evaluated. While the first approach should be to obtain clinic readings on more than one occasion, it may be helpful to supplement these with ambulatory recordings.

4.2.2 Disparity Between Clinic and Home Pressures

In any hypertensive patient the finding of a major disparity between clinic and home readings (e.g., more than 15 mm Hg) poses the question: which set of readings is closer to the true blood pressure? This can be resolved by an ambulatory recording.

4.2.3 Evaluation of Resistant Hypertension

The patient whose clinic pressures remain obdurately high despite being prescribed multiple medications presents a not uncommon clinical problem. While in some cases this may be the result of a genuinely resistant hypertension, in others it may be due to noncompliance or to an exaggerated white coat effect. The best clue to exaggerated white coat effect is a persistently elevated clinic pressure in the absence of target organ damage. Such patients can be evaluated either with ambulatory monitoring, or initially with home monitoring.

A less well described phenomenon is cuff inflation hypertension, in which the actual inflation of the cuff is accompanied by an increase of blood pressure.

Another cause of refractory hypertension is the sleep apnea syndrome (see Section 4.3.4). A clue to this may be that although the average level of blood pressure and heart rate fall during the night, their variability increases.[131]

4.2.4 Intermittent Symptoms Possibly Related to Blood Pressure

Episodes of lightheadedness, particularly in patients who are on antihypertensive medication, may be a manifestation of transient hypotension. This can readily be detected by ambulatory monitoring. If such episodes are of brief duration, however, they may be missed if readings are taken every 15 minutes.

4.2.5 Episodic Hypertension

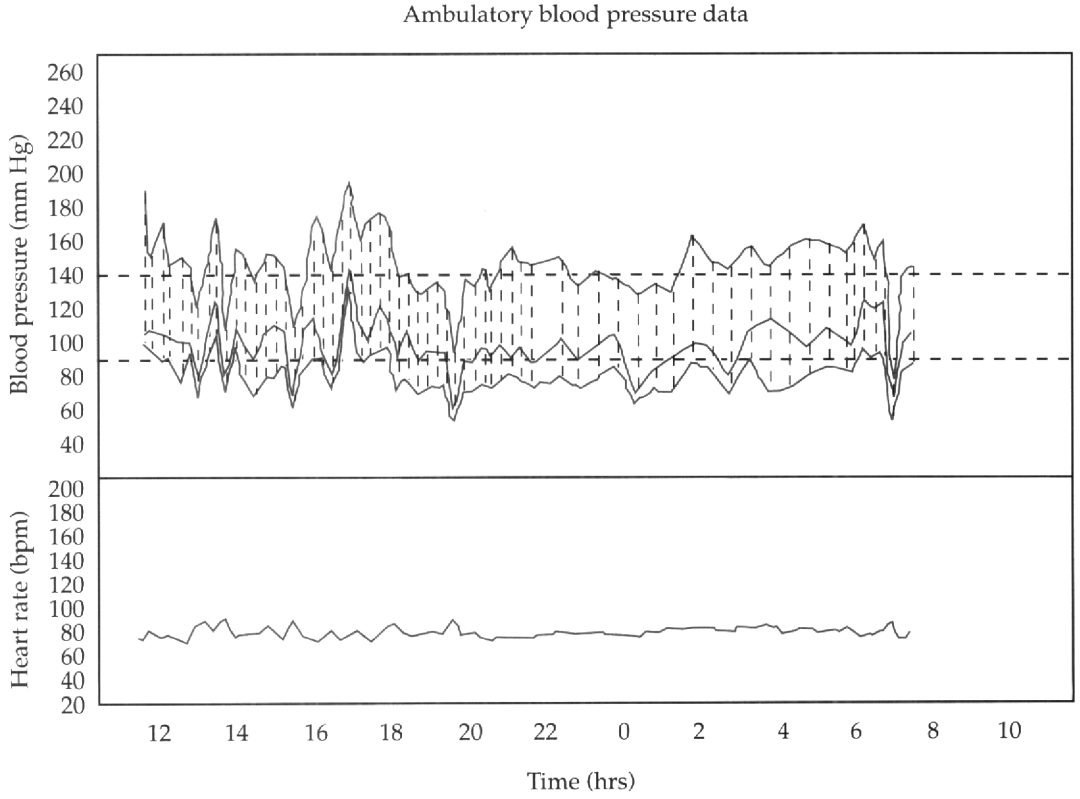
Episodic symptoms accompanied by transient elevations of blood pressure may occur in a variety of conditions. The use of ambulatory monitoring to demonstrate these episodes has been reported in patients with pheochromocytoma or panic attacks.[132]

4.2.6 Orthostatic Hypotension/Autonomic Neuropathy

In cases of orthostatic hypotension, ambulatory monitoring may be extremely helpful because many patients who are orthostatic during the day are hypertensive during the night (an example of this is shown in Figure 4.5).[133] There are huge swings of blood pressure during the day, depending to a large extent on changes of physical activity, and relatively stable but high pressures at night. In marked contrast, heart rate is relatively constant throughout the day and night.

Treatment of such patients usually involves giving pressor drugs, which while alleviating orthostatic hypotension may exacerbate nocturnal hypertension. Thus optimal treatment requires a balance between the two, which can only be properly evaluated with ambulatory monitoring. Patients with hypertension and diabetic autonomic neuropathy may also benefit from such an evaluation, which may demonstrate a paroxysmal elevation of pressure during the night.

Figure 4.5 — Diurnal profile of blood pressure and heart rate in a patient with orthostatic hypotension. Note hypotensive periods during the day, hypertension at night, and relatively fixed heart rate.



4.3 Ambulatory Blood Pressure in Patients with Sustained Hypertension

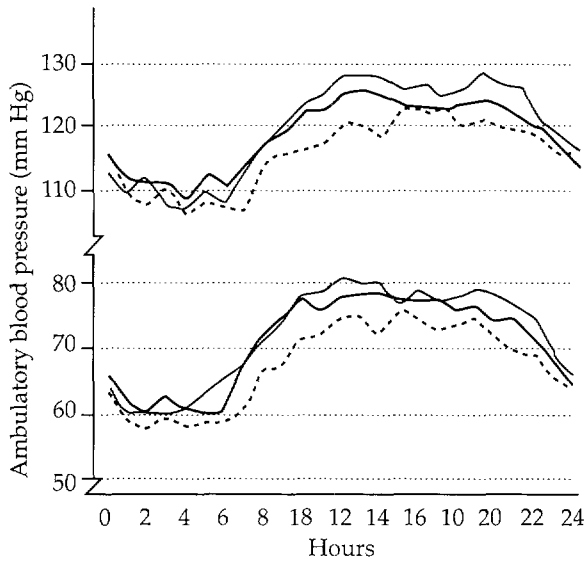
4.3.1 Essential Hypertension

In patients with essential hypertension the diurnal pattern of blood pressure change is generally similar to the changes occurring in normotensive subjects, except that the entire blood pressure profile is shifted upward (Figure 2.7). Thus, the differences between work and home pressures and between home and sleep pressures are approximately the same in normotensive and hypertensive subjects (approximately a 20% decrease during sleep in both cases) when expressed on a percentage basis, although in absolute terms they may be greater in hypertensives.[134] As described above, hypertensive patients can be subdivided into those who are dippers and nondippers, although this distinction is of little clinical relevance at the present time.

4.3.2 Family History of Hypertension

Children of hypertensive parents, who are still normotensive, show a slightly higher ABP than children of normotensives, but with a normal diurnal profile.[135] The elevation of pressure is greater during the day than at night, as shown in Figure 4.6.

Figure 4.6 — Comparison of diurnal ambulatory blood pressure (systolic and diastolic) in three groups of subjects: —— offspring of two normotensive parents, — — one normotensive and one hypertensive parent, and ···· two hypertensive parents.



4.3.3 Insulin Resistance Syndrome

It is well recognized that the combination of essential hypertension, insulin resistance, obesity, and hyperlipidemia carry an adverse prognosis. Many of these patients also have albuminuria, in which case there is likely to be a diminished nocturnal fall of pressure.[136]

4.3.4 Sleep Disordered Breathing and Sleep Apnea Syndrome

A wide spectrum of severity of sleep disordered breathing has been recognized, with snoring at the benign extreme, and obstructive sleep apnea at the other. These conditions are relevant to the present discussion not only because they affect the changes of blood pressure occurring during sleep, but also because they are significant risk factors for cardiovascular disease.

Sleep apnea syndrome is a condition that is probably under-diagnosed. The main reason for this is that at the present time its diagnosis requires an all-night study in a specialized sleep laboratory. It mainly affects middle-aged men, and its hallmark is episodic and repetitive apneic episodes occurring throughout the night. Characteristic symptoms include daytime sleepiness, snoring, disturbed sleep, morning headaches, fatigue, and impotence.[137]

The sleep apnea syndrome is conventionally defined by the presence of at least ten apneic episodes per hour (or sometimes 30 per night) lasting 10 seconds or longer. Minor degrees of sleep apnea are not uncommon in normal men, but are quite rare in women before menopause, although in postmenopausal women the incidence of sleep-disordered breathing resembles the incidence in men. Approximately 80% of individuals with sleep apnea syndrome are obese and approximately 80% are also hypertensive.[138,139] The prevalence of sleep apnea in hypertensive patients is also quite high — about 25%. It may be particularly common in patients whose hypertension is refractory to treatment. That the relationship between sleep apnea and blood pressure at night is a causal one has been suggested by the findings that tracheostomy or continuous positive airway pressure (CPAP), which relieves the apneic episodes, can also restore the normal nocturnal blood pressure fall, although the effects on daytime hypertension are less consistent.

During apneic episodes there is usually a transient increase of blood pressure, although it may decrease in elderly patients.[140]

4.3.5 Malignant Hypertension

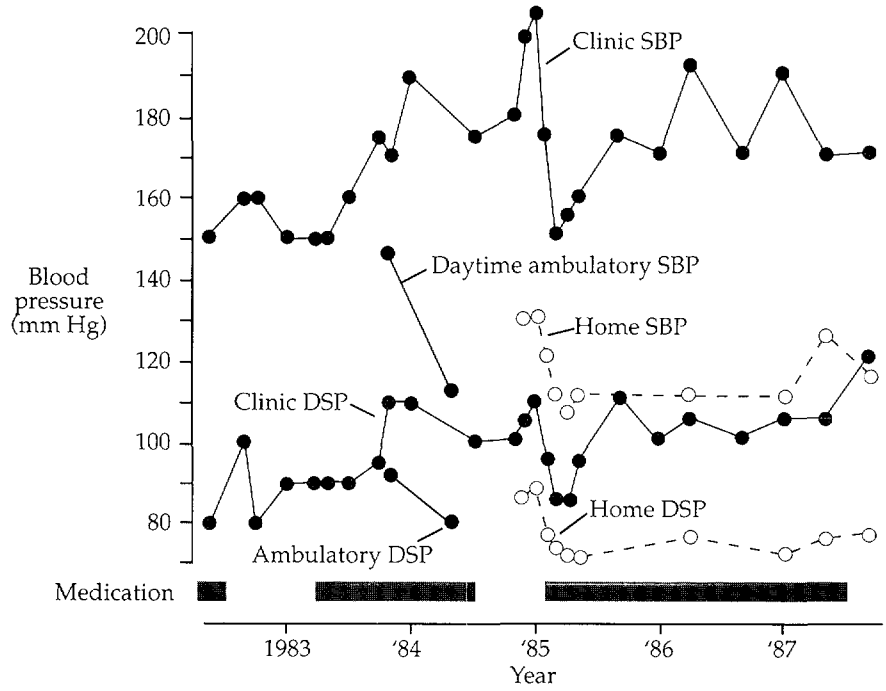
Ambulatory monitoring is not normally indicated for the evaluation of patients with malignant hypertension, where the diagnosis can be made from the routine clinical examination and where immediate treatment is of the highest priority. Nevertheless, it is interesting to note that there is a limited amount of evidence to indicate that malignant hypertension is characterized by an absent nocturnal fall of blood pressure.[141]

4.4 White Coat Hypertension

The term white coat hypertension has only come into common use in the last few years, but the idea is not a new one. It has been used to describe patients whose blood pressure is persistently elevated when measured in the physician's office or clinic, but normal at other times. An extreme example of this phenomenon is shown in Figure 4.7. This patient, a 64-year-old woman, had persistently elevated clinic pressures for several years, often reaching 180/120 mm Hg. Her home pressures, in contrast, had been as low as 120/80 mm Hg. That her technique of self-monitoring was accurate was demonstrated by having her take her own pressures in the clinic with her own machine, where she also recorded very high readings. Her ambulatory blood pressures were closer to the home pressures than to the clinic pressures and echocardiography revealed no evidence of target organ damage.

It has been suggested that such patients are at relatively low risk for cardiovascular morbidity and that pharmacological treatment of their blood pressure may be inappropriate. At the present time, there are two main areas of controversy relating to white coat hypertension — is it a benign condition? What are its origins?

Figure 4.7 — An example of white coat hypertension in a single patient. Note the persistent difference between clinic and home pressures.



4.4.1 Definition of White Coat Hypertension

The broad definition of white coat hypertension is a persistently elevated clinic blood pressure and a normal pressure at other times. It cannot be diagnosed simply on the basis of clinic and home pressures because the pressure might be high at work, for example. Its precise definition is inevitably arbitrary, like any other category of hypertension. It should be emphasized that it cannot be defined on the basis of a single clinic visit — many individuals have a relatively high blood pressure when first seen, which, as discussed above, decreases with repeated visits, either because of habituation to the clinic setting or regression to the mean. One commonly used criterion is a clinic pressure which remains elevated (above 140/90 mm Hg) on the second and third visits. To establish that the blood pressure is normal outside the clinic requires the use of ambulatory monitoring and the definition of a cutoff point for the upper limit of the normal range. Pickering et al. chose the 90th percentile of the daytime blood pressure (i.e., 134/90) as the upper limit based on recordings made in normal volunteers. To be classified as white coat hypertensives, the patients had to have both systolic and diastolic ambulatory pressures below these levels.[142]

It is important to stress that the criteria used to define white coat hypertension will be a major determinant of its prevalence — and also of its prognosis. Verdecchia et al. examined the question of the definition of white coat hypertension by comparing four different cutoff points for defining the upper range of normal ABP, taking levels proposed in previous studies (Table 4.1).[143-145] The prevalence of white coat hypertension differed markedly between the four methods, ranging from 12.1% using the lowest cutoff point to 53.2% using the highest. There were parallel changes in the prevalence of LVH ranging from 2.4 to 14.7% (see Table 4.1). The authors concluded that if white coat hypertension is to be regarded as a benign condition, more conservative definitions (such as the original cutoff point of 134/90 mm Hg) should be used.

Table 4.1 – Consequences of Different Criteria for Diagnosing White Coat Hypertension

Author	Reference	Percentile	Upper Limit of Normal	Prevalence of WCH	Prevalence with LVH
Verdecchia	143	90	136/87	12.1%	2.4%
Pickering	142	90	134/90	16.5%	3.5%
Staessen	144	95	146/91	28.9%	9.0%
O'Brien	145	95	150/95	53.2%	14.7%

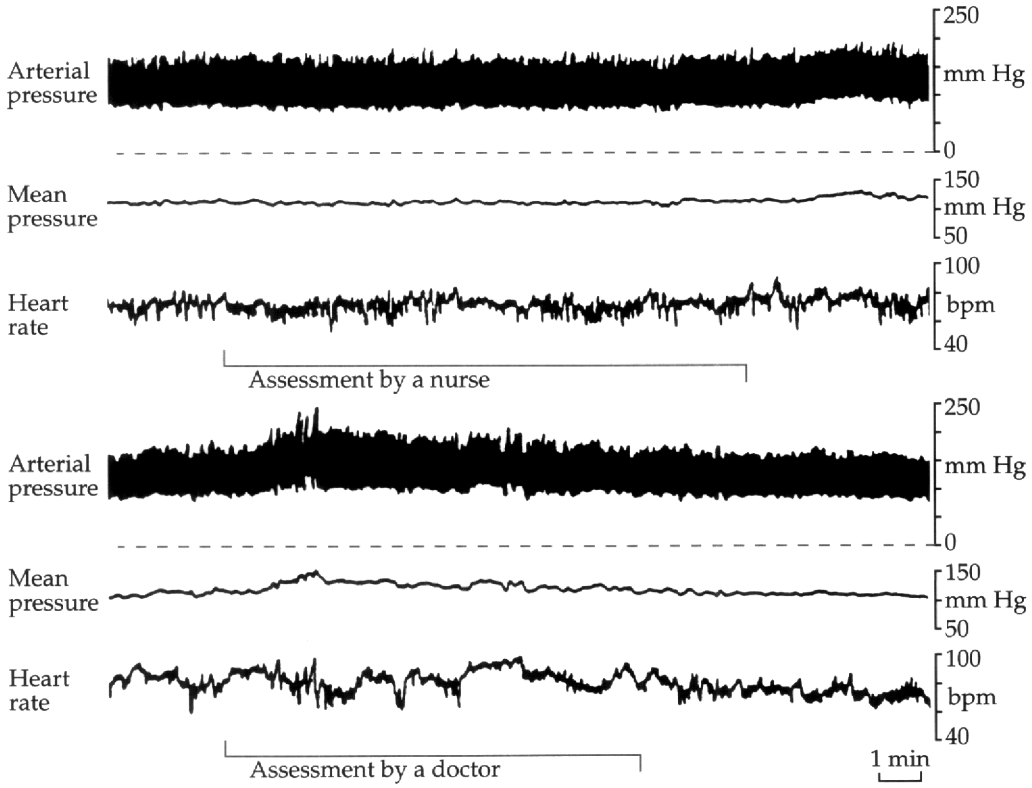
4.4.2 Prevalence of White Coat Hypertension

Depending on the criteria used for its definition, and the population being studied, the prevalence of white coat hypertension among patients with mild to moderate hypertension (diastolic pressures between 90 and 105 mm Hg) is about 20 to 40%. Similar values have been reported for both hospital-based and private practices.[146-148]

4.4.3 Demographic Factors Contributing to White Coat Hypertension

The prevalence of white coat hypertension has been found to be influenced by a number of demographic factors, including gender, age, and obesity. Whether or not race is also a factor remains to be seen. White coat hypertension tends to be somewhat more common in women than in men, but this has not been a universal finding. It is surprisingly common in patients over the age of 65, including those with isolated systolic hypertension, as described in Section 4.6. White coat hypertension may be less common in the obese, although this too has not been a universal finding.

Figure 4.8 — Continuous intra-arterial readings of blood pressure (A) taken from one arm while a nurse (upper traces) or a doctor (lower traces) took an auscultatory measurement of blood pressure from the other arm.



4.4.4 Psychological Factors Contributing to White Coat Hypertension

The influence of a physician's presence on the patient's blood pressure has been demonstrated most elegantly by the study of Mancia's group using continuous intra-arterial recording of pressure in hospitalized patients.[149,150] When the physician approached the patient and put a blood pressure cuff on the arm there was an immediate rise of pressure which lasted throughout the procedure of taking a reading, and then a gradual return to baseline over a period of several minutes. In another similar study, the average change of pressure evoked by the physician was 23/18 mm Hg, which was approximately twice as high as when the pressure was taken by a nurse, (see Figure 4.8).[149]

In the study of Pickering et al., clinic pressures were recorded not only by a physician (usually male) but also by a technician (usually female).[132] As shown in Table 4.2, the technician's readings were not only lower than the physician's, but also closer to the daytime average recorded during ambulatory monitoring.[151-153] These observations are consistent with the earlier findings of Mancia's group that physicians provoke a larger white coat effect than nurses.

Table 4.2 – Prevalence of White Coat Hypertension According to Different Diagnostic Criteria

Author (Reference)	Setting	No. of Patients	Diastolic Criterion <85 mm Hg	Diastolic Criterion <90 mm Hg
Pickering (142)	Clinic	292		21%
Zachariah (151)	Clinic	168		35%
Krakoff (146)	Clinic	60	38%	
Waeber (152)	Clinic	245		61%
Schnall (153)	Worksite	87	23%	39%
Khoury (147)	Private Practice	131	34%	52%
Hoegholm (148)	Clinic	159		25%

The personality of the patient is another potential factor. It might be expected that patients who show the white coat effect would be generally more anxious, but this is not necessarily the case. So far there has been no demonstration of any consistent difference in anxiety levels between patients with white coat or sustained hypertension.[154]

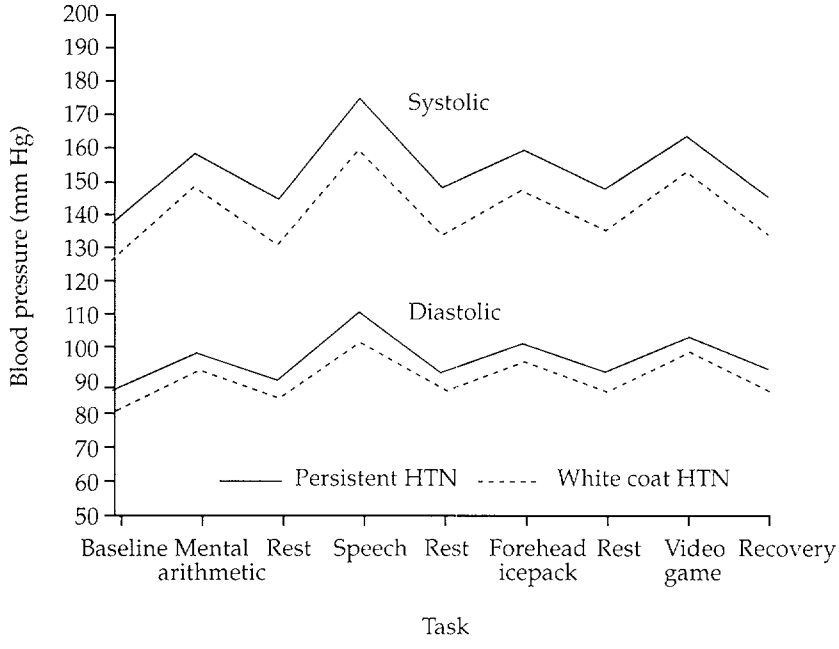
4.4.5 Physiological Factors Contributing to White Coat Hypertension

White coat hypertension does not appear to be characterized by a generalized increase of blood pressure reactivity to stress, because ambulatory recordings show no increased blood pressure variability in white coat hypertensives, and no exaggerated increase of blood pressure while at work in comparison to normotensives or with patients with sustained hypertension. This view is supported by studies in which the blood pressure reactivity to laboratory stressors has been compared in subjects with white coat and sustained hypertension and generally found to be no different.[155,156] An example of this is shown in Figure 4.9.

Several studies using ambulatory monitoring have found no greater variability of blood pressure over 24 hours in white coat hypertensives as compared to patients with sustained hypertension or normotensive controls.[132,154,155] Thus, none of these studies offers any support to the idea that the white coat effect is a manifestation of a generalized cardiovascular hyperactivity.

The sensitivity of the baroreceptor reflexes is one factor which regulates the blood pressure response to an acute pressor stimulus (e.g., a physician), such that a larger response would be elicited in patients with less sensitive reflexes. However, it has been reported that subjects with white coat hypertension have a higher baroreflex sensitivity than those with sustained hypertension. Since a reduced reflex sensitivity is a consequence of sustained hypertension, this finding would also be consistent with a generally normal cardiovascular system in patients with white coat hypertension.

Figure 4.9 — Comparison of reactivity to laboratory stressors in patients with sustained or white coat hypertension.



There is also some indirect evidence that sympathetic nervous activity is normal, as evaluated by heart rate, plasma norepinephrine, and urinary catecholamine excretion.[156,158]

4.4.6 Mechanisms Underlying White Coat Hypertension

At least three mechanisms have been postulated to explain white coat hypertension. The first is that it represents an exaggerated alerting or orienting response and, thus, a generalized hyperactivity to novel or stressful stimuli. The second is that it is a precursor of sustained hypertension, which could be in association with hyperactivity, or independent of it. The third mechanism which has been advocated is that it is a learned or conditioned response.

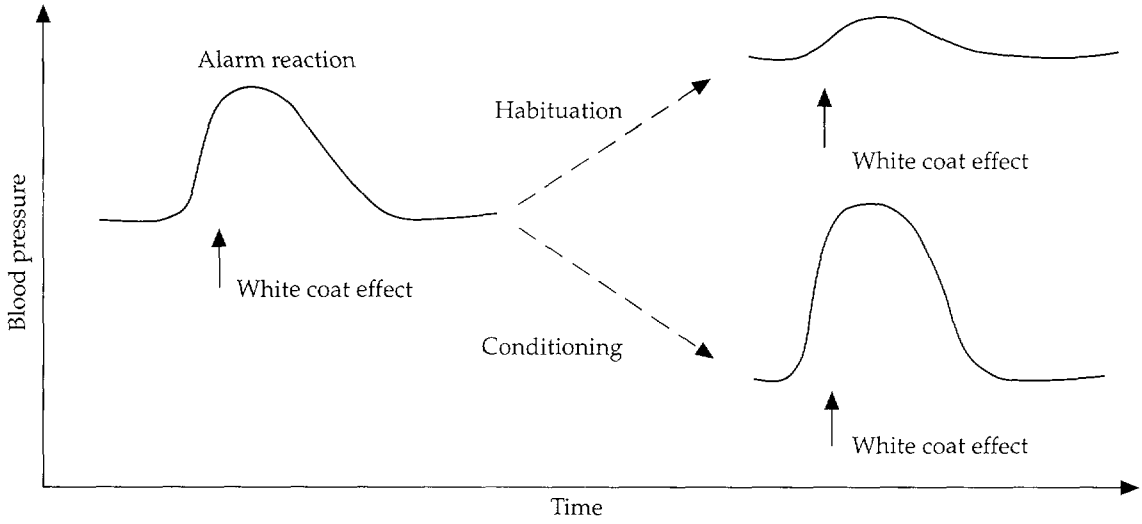
As already seen, the bulk of the evidence does not support the view that it represents a generalized hyperactivity. While the possibility that it is a precursor of essential hypertension cannot be excluded, the fact that it tends to be more, rather than less, common in older patients would argue against this. The white coat effect appears to be just as large in patients with renovascular hypertension as in essential hypertension, which one would expect if it is an acquired phenomenon.[159]

An alternative explanation is that while the white coat effect originates as part of the defense reflex, it becomes perpetuated through classical conditioning. The subject who initially exhibits a large pressor response is told by the physician that his or her blood pressure is a matter of concern and needs to be rechecked. The initial unconditioned stimulus, which is the unpleasant and novel situation promoting the innate and unconditioned response of fear, leads to an increased blood pressure. The patient learns to associate the physician as the harbinger of bad news, who thus becomes a conditioned stimulus who continues to elicit the pressor response in the patient. Thus, the normal process of habituation, which results in a diminution of the alerting response to repeat visits, does not occur.

The two contrasting patterns — habituation leading to a diminution of the defense or orienting response, and conditioning leading to a perpetuation of it as the white coat effect — are illustrated schematically in Figure 4.10.

A Norwegian study supports this proposed mechanism.[160] Twenty-nine young men who were found to have elevated blood pressures on a routine examination were randomly divided into two groups. The first was sent a letter telling them that their pressure was too high, and the second a neutral letter. On the second examination the blood pressure in the first group was 16/10 mm Hg higher than in the second group throughout a 45-minute testing period.

Figure 4.10 — Hypothetical development of the white coat effect. When blood pressure is first taken there is a pressor response due to the orienting or defense response. In the majority of patients this habituates with repeated exposure, but in some it may become perpetuated as a conditioned response.



4.4.7 Is White Coat Hypertension a Benign Condition?

From a clinician's point of view, the most important question is whether or not white coat hypertension can be considered a benign condition. At the present time there are two opposing views: the majority of investigators consider the prognosis to be benign, while a minority have suggested that the risk in white coat hypertension is similar to the risk of patients with sustained hypertension. Evidence for both of these views is reviewed below.

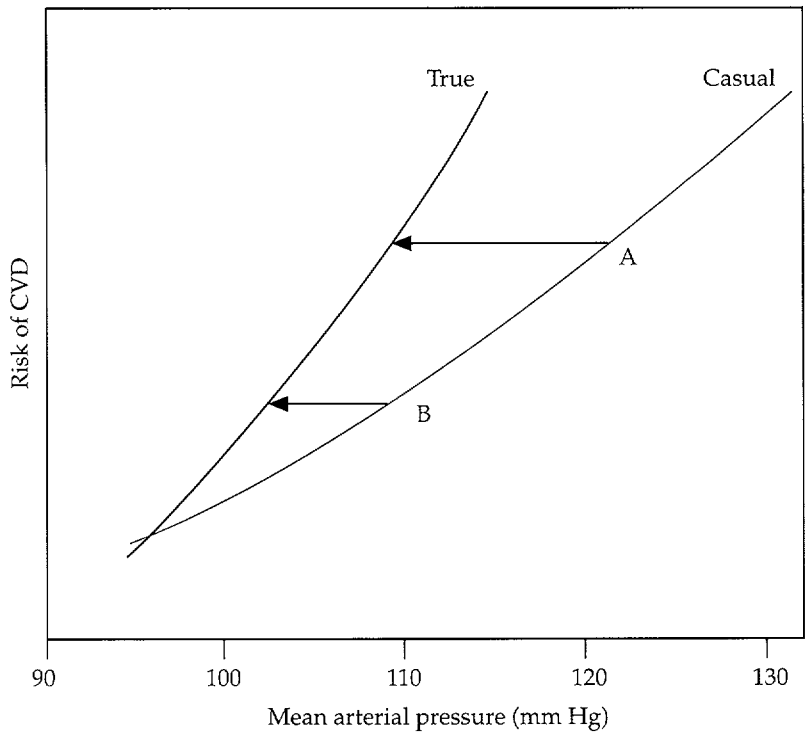
The crux of the argument concerns which measure of blood pressure gives the best indication of risk of cardiovascular morbidity. It is well recognized, from studies such as the Framingham Heart Study, that casual or clinic blood pressure measurements tend to show the phenomenon of regression to the mean, such that individuals whose pressure is initially recorded as high will show a decrease with time, while those with low initial pressure will show an increase. Thus, at high levels of clinic pressure, true blood pressure is overestimated, while at low levels it is underestimated and the relationship between blood pressure and risk will, therefore, be steeper for the true pressure than for the casual pressure (Figure 4.11).

The evidence supporting the view that white coat hypertension is benign is not conclusive, but is generally supportive. The only prospective study of morbidity related to ambulatory pressures so far to be published was conducted by Perloff et al.[161,162] Although they did not attempt to define a subgroup with white coat hypertension, they found that patients whose ambulatory pressures were low relative to their clinic pressure were at lower risk than those with higher ambulatory pressures. Am-

bulatory pressures added to the prognostic value of clinic pressure in patients who were under 50 years, had an initial diastolic pressure below 105 mm Hg, and had no prior morbid events. These are all characteristics which we would associate with white coat hypertension. In older patients with more advanced hypertension, the ambulatory pressures were not of additional value over the clinic pressures. There is also evidence that, for the same level of clinic pressure, target organ damage is less pronounced in patients with white coat than with sustained hypertension.[163-165]

An opposing view, that white coat hypertension is not a benign condition, has been expressed by Julius et al. on the basis of their findings in a population study of 737 young adults in Tecumseh, Michigan, whose blood pressure was evaluated by home and clinic readings.[166] No ambulatory monitoring was performed. They were classified as normotensive (both measures normal), sustained hypertensive (both raised), or white coat hypertensives (only the clinic pressures raised). Using Julius's criteria, 58% of the hypertensives had white coat hypertension and also showed a high prevalence of the metabolic abnormalities which accompany hypertension (e.g., faster heart rates, higher systemic vascular resistance, hyperinsulinemia, and hypertriglyceridemia). However, this conclusion derived from their choice of cutoff point, which may have resulted in the inclusion of many true hypertensives in the

Figure 4.11 — Hypothetical relationship between casual (or clinic) and true (or ambulatory) blood pressure and risk of cardiovascular disease. The units of risk are arbitrary. Note that patient A, who is more severely hypertensive than patient B, shows a larger difference between casual and true blood pressures.



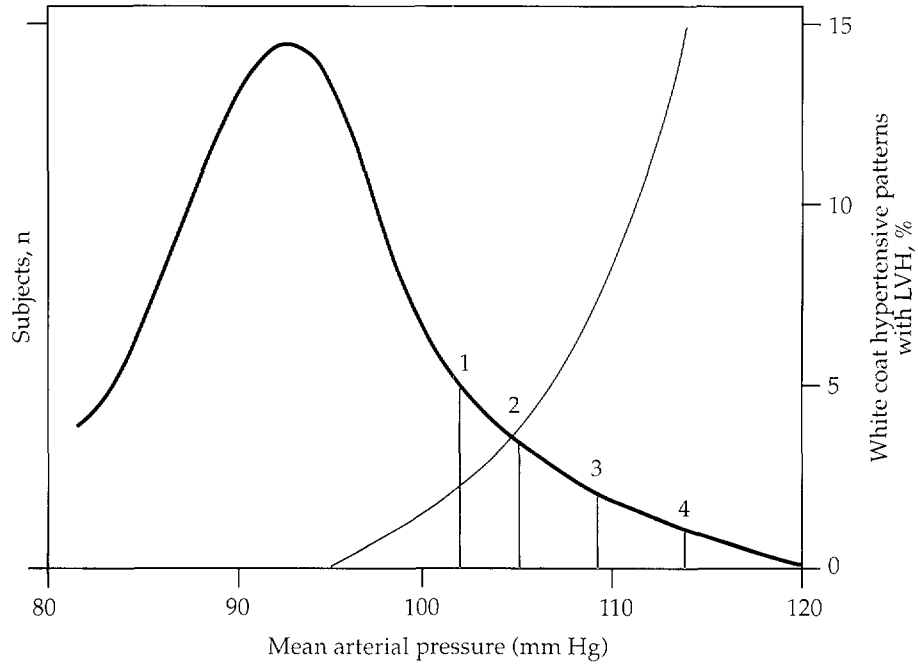
white coat group. As shown in Figure 4.12, a cutoff point that gives a higher prevalence of white coat hypertension will include a higher proportion of patients with target organ damage.

4.5 Ambulatory Blood Pressure Measurement in the Elderly

The variability of blood pressure increases in elderly patients. The daytime variability of blood pressure may also be greater in patients with isolated systolic hypertension than in those with diastolic hypertension.[167] In contrast, the variability of heart rate is decreased. This may be explained by a diminution of baroreflex sensitivity with aging, and an inability to buffer blood pressure change either by changes in peripheral resistance or heart rate. Another important factor influencing blood pressure variability in the elderly is their level of activity — variability during the day is greater in patients who are ambulatory than in those who are bedridden.[168] While increased physical activity might be expected to raise pressure in younger patients, in the elderly there may also be episodes of decreased pressure from orthostatic hypotension. Whether this increased blood pressure variability contributes to morbidity independent of the level of pressure remains uncertain.

Most investigators have found that the amplitude of the nocturnal fall of blood pressure is similar in younger and older subjects, while in patients with isolated sys-

Figure 4.12 — Distribution of blood pressure in the general population (black), and percentage of white coat hypertensives with LVH (color). The numbers above the vertical lines show four different cutoff points used to define white coat hypertension.



tolic hypertension it may be exaggerated in comparison with essential hypertensive or normotensive subjects of the same age.[167,169]

4.5.1 White Coat Hypertension in the Elderly

Several studies have reported that white coat hypertension is at least as common in the elderly, including patients with isolated systolic hypertension, as in younger patients. Furthermore, there is less correlation between clinic and ambulatory pressures in older than in younger subjects.

4.5.2 Prognostic Significance of Ambulatory Blood Pressure in the Elderly

The ultimate proof of the utility of ambulatory monitoring in elderly patients would be the demonstration that it improves the prediction of risk. So far, data on this is lacking. In the original paper on their prognostic study, Perloff et al. noted that daytime ABP did not improve the prediction of risk in patients over the age of 50, although it did in younger patients. However, there is some evidence that, as in younger patients, ABP correlates more closely with the extent of silent cerebrovascular disease (measured as lacunae on a magnetic resonance image) than clinic pressure.[170]

4.5.3 Evaluating the Need for Antihypertensive Therapy in Elderly Hypertensives

Excessive reduction of blood pressure may be hazardous in elderly hypertensive patients because of problems such as orthostatic hypotension and postprandial hypotension, both of which are common in older people. A retrospective analysis of elderly hypertensives showed that there was no significant improvement in blood pressure control by increasing or initiating antihypertensive drug treatment when clinic pressures were high in comparison to ambulatory pressures (i.e., white coat hypertensives); this was in contrast to patients with sustained hypertension (i.e., ABP and clinic pressure high) in whom treatment lowered the ABP.[171] These results were confirmed prospectively in a study of 18 patients over the age of 70 — only the patients with an initial elevation of both clinic and ABP responded with a decrease of ABP.[172]

4.6 Ambulatory Monitoring in Patients with Secondary Hypertension

Several types of secondary hypertension, described below, are associated with an absence of the normal nocturnal fall of blood pressure, and it has even been suggested that the discovery that a particular patient is a nondipper may indicate the possibility of a secondary origin for the hypertension.[173] However, this is a very nonspecific finding; many patients with essential hypertension may be nondippers, and many with secondary hypertension are dippers. Ambulatory monitoring is therefore not recommended for the routine evaluation of secondary hypertension.

4.6.1 Renovascular Hypertension

Patients with the most common type of secondary hypertension, renovascular hypertension, have not been found to show any consistent differences in the diurnal rhythm of blood pressure when compared with essential hypertensives.[174]

4.6.2 Chronic Renal Disease

Patients with chronic renal disease tend to be nondippers, although the decrease of heart rate is still present, if somewhat attenuated.[175] There may be an element of autonomic neuropathy, and baroreflex sensitivity is impaired in such patients. In patients with transplanted kidneys, prednisone therapy is another contributing factor.

4.6.3 Pheochromocytoma

Patients in whom pheochromocytoma is suspected are obvious candidates for ABP monitoring. The classic paroxysmal elevations of blood pressure have been detected in about 25% of 24-hour studies of patients in whom the diagnosis is proven[59], so that it may be necessary to study these patients more than just occasionally to detect them. Some patients may show an absent nocturnal fall of blood pressure, but this is by no means universal. There have been occasional reports of cyclical variations of blood pressure in patients with pheochromocytoma ranging from 240/140 to 100/80 mm Hg every five to ten minutes.[177,178] The increases of pressure are accompanied by a reflex bradycardia and maybe related to dehydration.

4.6.4 Cushing's Syndrome

In Cushing's Syndrome the normal nocturnal fall of blood pressure is absent, although the usual decrease of heart rate persists.[179] Blood pressure gradually rises between midnight and early morning, reaching a peak at about the time of waking. This phenomenon is attributable to the excess of glucorticoids, since patients with chronic glomerulonephritis or systemic lupus erythematosus also have no nocturnal fall of blood pressure when treated with prednisone, but a normal fall when untreated (see Figure 4.13).[180] The diurnal rhythm of heart rate is unaffected by glucocorticoids in these patients.

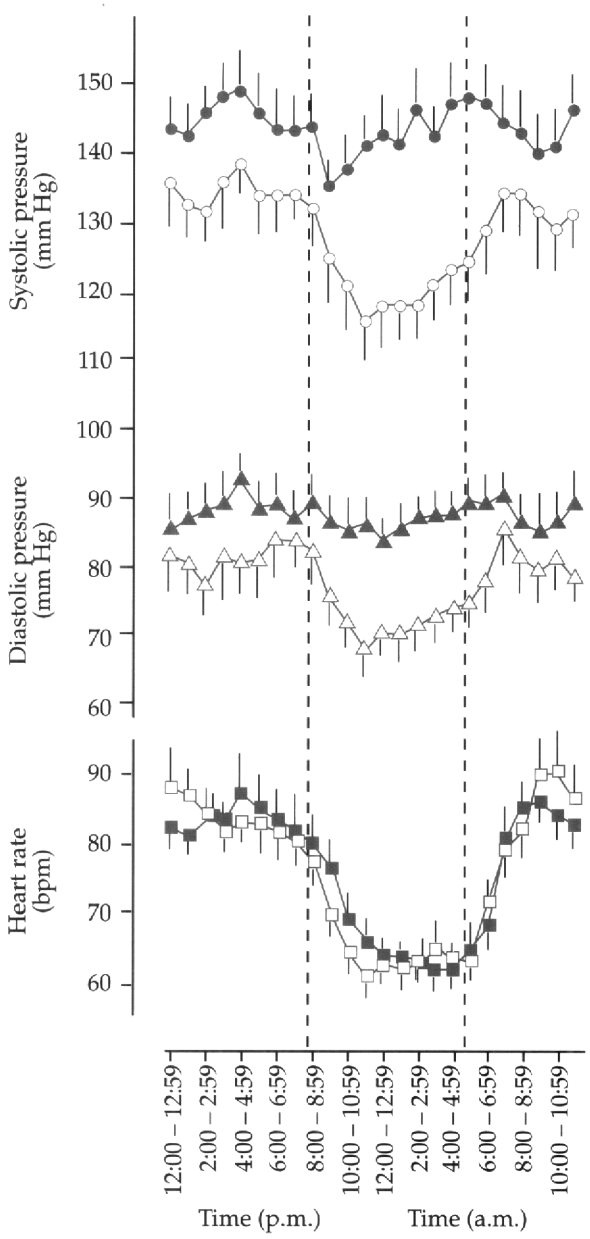
4.6.5 Hyperaldosteronism

The diurnal rhythm of blood pressure has been found to be normal in patients with primary aldosteronism.[181]

4.7 Ambulatory Monitoring for the Evaluation of Episodic Blood Pressure Changes

Ambulatory monitoring is of limited value for the diagnosis of paroxysmal hypertension, as exemplified by pheochromocytoma, but is of considerable use in the evaluation of patients who show orthostatic blood pressure changes on routine clinical examination.

Figure 4.13 — Effects of prednisone administration on the diurnal rhythm of blood pressure in patients with chronic renal disease: untreated (○, △, □) and treated with prednisone (●, ▲, ■).



4.7.1 Orthostatic Hypotension

Patients suffering from idiopathic orthostatic hypotension have been found to exhibit a paradoxical elevation of pressure during the first part of the night, and the lowest pressures of the day during the morning, when they are typically most symptomatic.[182] These pressure changes are associated with less consistent changes of heart rate, which may decrease during the night, or show little change. The nocturnal rise

of pressure cannot be explained purely on the basis of recumbency, because it is still seen in patients who are recumbent for the full 24 hours. The hypotensive episodes occur with the upright position, or after meals.

Orthostatic hypotension is also a feature of the Shy-Drager syndrome, which differs from idiopathic orthostatic hypotension in that there are also sphincter disturbances and Parkinsonian features. Some of these patients may also have sleep apnea, but even in those who do not, the blood pressure increases during the night.[183]

4.7.2 Diabetes Mellitus with Autonomic Neuropathy

Autonomic neuropathy is a not uncommon complication of insulin-dependent (type I) diabetes, and has been attributed to interruption of both vagal and sympathetic control of the circulation. The former is manifested by a relatively fixed heart rate, and the latter by orthostatic hypotension. In common with patients with idiopathic orthostatic hypotension, blood pressure remains high during the night.[184] This is seen particularly in patients with microalbuminuria.[127]

4.8 Ambulatory Monitoring in Normotensive Conditions

The clinical conditions described below are not ones where ambulatory monitoring would normally be appropriate, but are included because they are characterized by an absent nocturnal blood pressure decrease.

4.8.1 Congestive Heart Failure

In patients with congestive heart failure, it has been reported that neither blood pressure nor heart rate show much change during the night, particularly in those with the lowest ejection fractions.[185]

4.8.2 Cardiac Transplantation

Cardiac denervation is another situation where pressure increases at night. This has been observed in patients with cardiac transplants.[186] The nocturnal bradycardia is still present. The mechanism is unexplained, but could in part be due to increased venous filling of the heart associated with recumbency.

4.8.3 Hyperthyroidism

Although this is not a disease which would normally be evaluated by ambulatory monitoring for clinical reasons, it is of interest to note that it is one of the conditions associated with an absent nocturnal fall of blood pressure.[177]

5.0 AMBULATORY BLOOD PRESSURE MONITORING IN CHILDREN

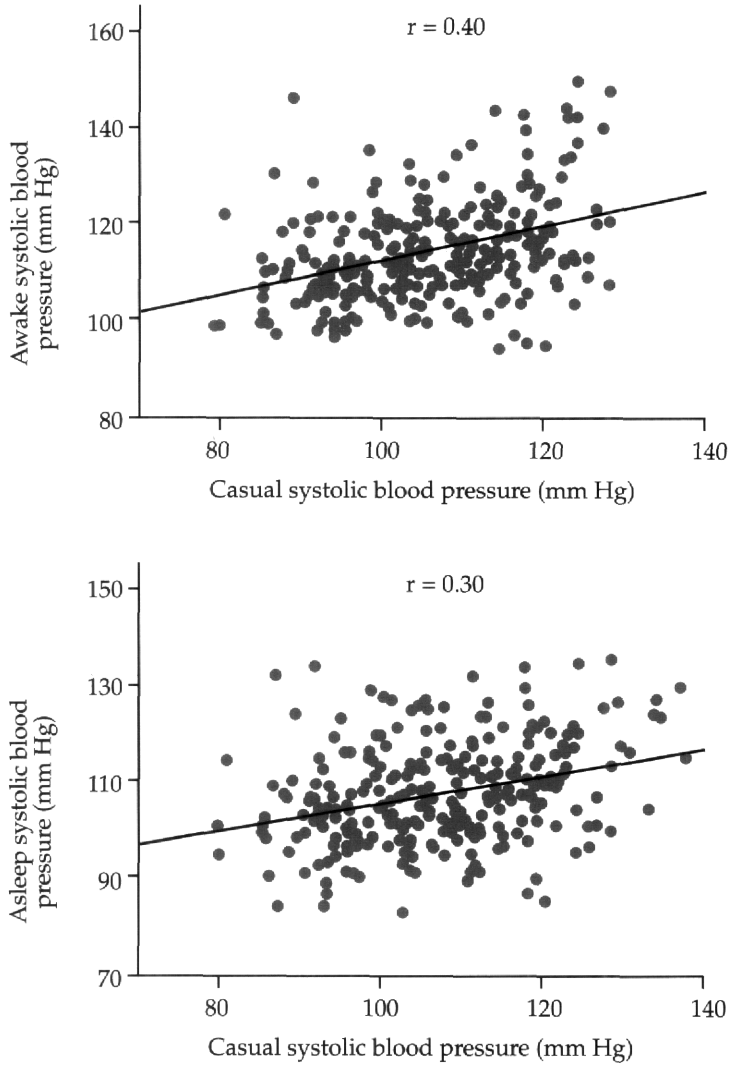
The origins of essential hypertension begin in childhood. Many investigators are attempting to identify, in children and adolescents, markers or mechanisms of later onset essential hypertension in high-risk populations. One of the areas of study has been the pattern of ABP. Monitoring of ABP may allow recognition of abnormalities in the high-risk population, such as reduced nocturnal decline of blood pressure, which could be utilized in studies of the mechanism(s) of evolution of essential hypertension, and as a basis for interventions to lead to a primary prevention. If hypertension could be avoided rather than treated, the healthcare costs of the United States population would be significantly reduced. For these reasons, ABP monitoring has evolved as a research tool in selective laboratories. The data described later in this section could be utilized by the primary care provider whether the blood pressure of an individual patient is, or is not, normal.

5.1 *The Relationship Between Casual Blood Pressure and Ambulatory Blood Pressure*

It has already been pointed out that there is a weak relationship between casual blood pressure and ABP in adults, and this is true for children and adolescents as well. Figures 5.1 and 5.2 show these relationships for both systolic and diastolic blood pressure in a study by Harshfield et al. of 300 normotensive children and adolescents. Although all of the correlations were statistically significant, the level of the correlations indicate that casual blood pressure cannot be used as an alternative to ABP monitoring in youths as in adults.[188] For example, children with a casual systolic blood pressure between 100 and 120 mm Hg had a mean awake ambulatory systolic blood pressure between 91 and 143 mm Hg. This is a range of 52 mm Hg in awake ambulatory systolic blood pressure which was associated with a range of 20 mm Hg in casual blood pressure. Also, these children had an asleep mean systolic blood pressure between 75 and 133 mm Hg, a range of 58 mm Hg.

The situation was similar for diastolic blood pressure. For example, children with a casual diastolic blood pressure between 60 and 80 mm Hg (a difference of 20 mm Hg) had an awake ambulatory diastolic blood pressure between 51 and 83 mm Hg, a difference of 32 mm Hg. Also, these children had an asleep ambulatory diastolic blood pressure between 42 and 81 mm Hg, a difference of 39 mm Hg associated with the 20 mm Hg difference.

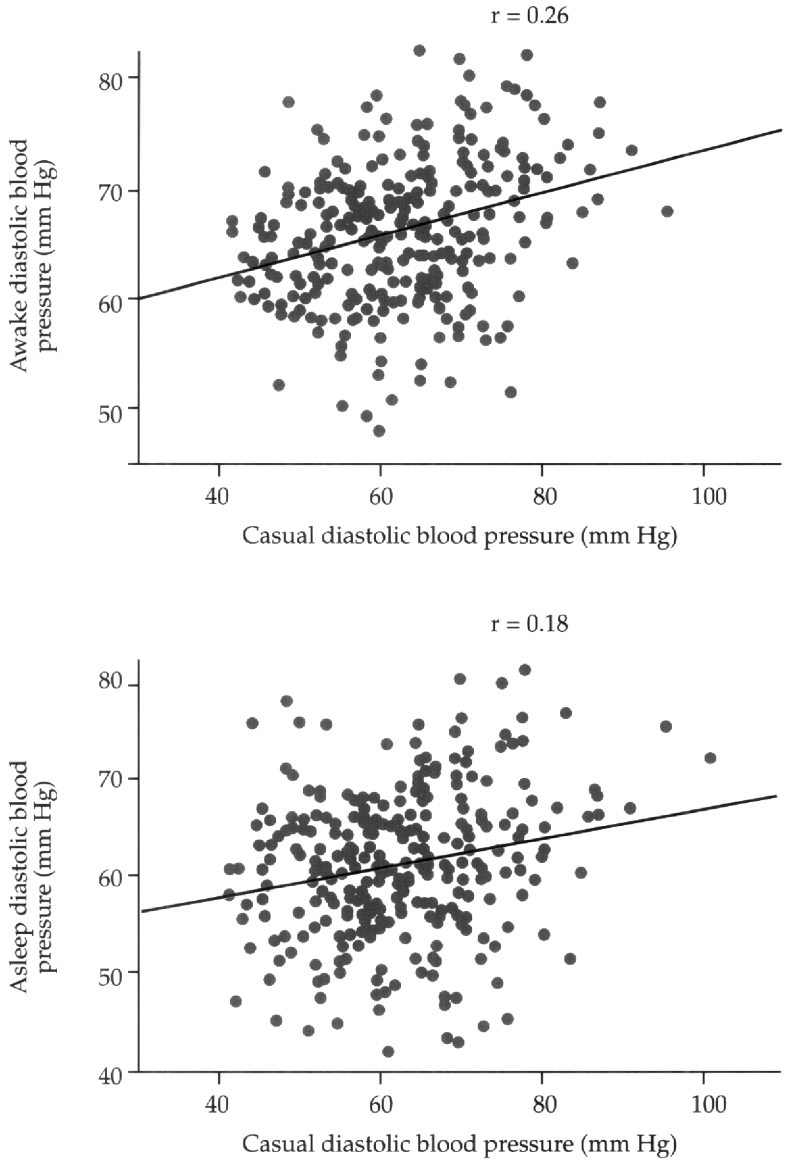
Figure 5.1 — Relationship between casual and ambulatory systolic blood pressure in 300 normotensive children and adolescents.



5.2 Ambulatory Blood Pressure Norms in Youths

Initially, the lack of reference data on normal individuals limited the utility and acceptance of ABP monitoring. As presented in Section 4.0, these data are now available for adults with the publication of numerous large studies. However, there are very few studies of ABP monitoring in normal, healthy children and adolescents. The largest study to date is that published by Harshfield et al.[188] As shown in Figure 5.3, ambulatory systolic blood pressure was higher for boys compared to girls both while awake and during sleep. In contrast, ambulatory diastolic blood pressure while awake and during sleep was similar for boys and girls.

Figure 5.2 — Relationship between casual and ambulatory diastolic blood pressure in 300 normotensive children and adolescents.



Age was a factor in the difference in systolic blood pressure both while awake and during sleep, as shown in Table 5.1. Comparisons between boys and girls within age groups showed that boys in the 10 to 12 years of age group had higher systolic blood pressure while awake as compared to girls in the same age group. In the 13 to 15 years of age group, boys had higher systolic blood pressures while awake. In the 16 to 18 years of age group, boys had higher systolic blood pressure while awake and during sleep.

Figure 5.3 — Ambulatory systolic blood pressure in boys and girls while awake and during sleep.

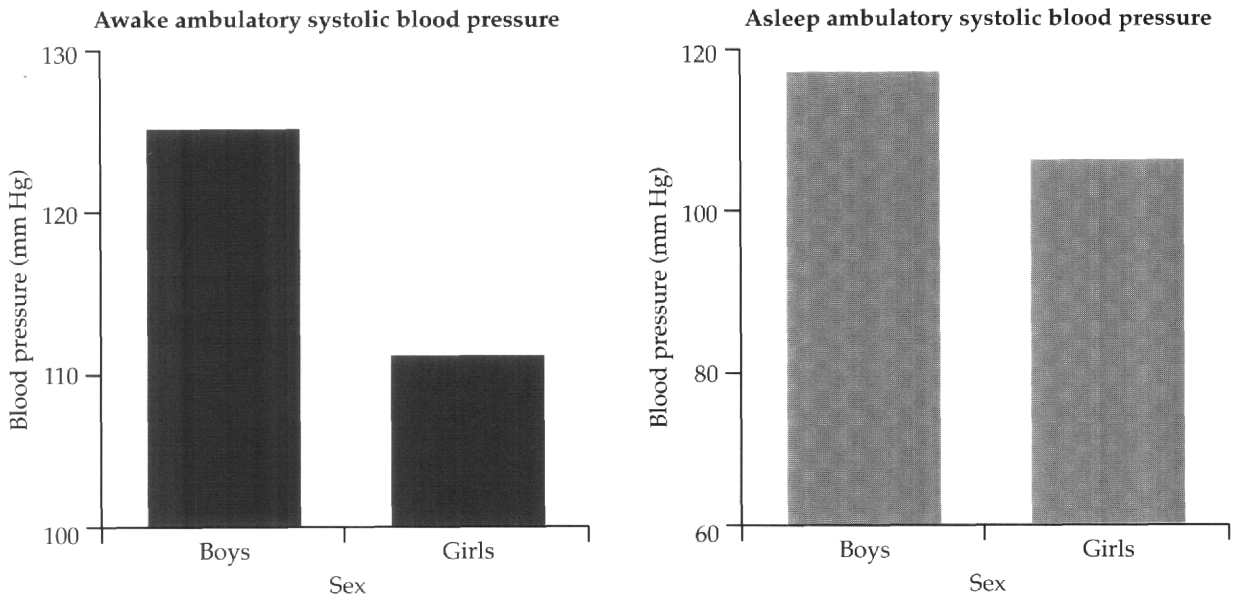


Table 5.1 – Median (interquartile range) for Awake and Asleep Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) by Sex and Age Group

	Boys			
	Awake		Asleep	
Age (n)	SBP (mm Hg)	DBP (mm Hg)	SBP (mm Hg)	DBP (mm Hg)
10 to 12 (71)	115 (109, 120)	67 (60, 72)	107 (99, 114)	61 (55, 66)
13 to 15 (59)	116 (108, 122)	65 (61, 69)	108 (101, 107)	61 (56, 66)
16 to 18 (30)	125 (114, 134)	69 (64, 72)	117 (111, 123)	63 (52, 67)
	Girls			
10 to 12 (55)	112 (105, 117)	65 (61, 67)	105 (100, 111)	60 (56, 64)
13 to 15 (43)	112 (106, 118)	66 (60, 71)	105 (98, 113)	60 (54, 66)
16 to 18 (42)	111 (105, 120)	70 (66, 74)	106 (101, 109)	65 (60, 71)

5.3 Technical Issues

Automatic, noninvasive ambulatory monitoring has been used in the adult population for both research and clinical purposes for the last 15 years. Only recently has the use of ABP monitoring received acceptance in the pediatric population, and this has been primarily in the research setting. There are several reasons for this. Perhaps the primary reason is the low prevalence of essential hypertension among children and adolescents. Most forms of hypertension in youths are secondary to a known cause. As a result, pediatricians could not justify the expense of an ABP monitoring system. These expenses included the cost of the recorders, the computer to read the recorders, the supplies, and the service contracts for the recorders. In addition, a full-time technician was needed to attach the recorders, retrieve the data, and generate a patient report. A second reason is that the initial studies on ABP monitoring in youths were discouraging. In part, this was because the first recorders were designed for adults. Small cuffs were not available, leading to problems with the calibration of the recorders. The recorders were bulky and loud, so the children did not tolerate them well. Finally, the recorders were very sensitive to movement and the children had a difficult time relaxing their arm during a blood pressure determination, thus resulting in very large numbers of artifactual readings.

Ambulatory blood pressure monitoring is now a viable technique for use in children and adolescents. The new generation of ABP recorders are far superior to the early recorders. They are smaller and quieter, so children tolerate them much better. In addition, they are less expensive, more reliable, and provide extensive patient reports reducing cost in terms of both money and manpower.

5.4 Evaluation of Elevation of Casual Blood Pressure — White Coat Hypertension

Similar to adults, children with elevated blood pressure may be studied with 24-hour ABP monitoring to define whether their pressures outside the physician's office are elevated or normal (white coat hypertension). If elevated, how high do the blood pressure values rise during normal daily activities? The ABP monitoring pattern in hypertensive adults has been shown to be more predictive of target organ damage than the casual blood pressure; similar data would be of great clinical use to decide upon therapy options for hypertensive children and adolescents.

In a parallel fashion, children of hypertensive parent(s) who have high normal or borderline elevation of blood pressure may undergo 24-hour ABP monitoring to assess whether their 24-hour blood pressure profile is high risk, i.e., do they show persistent nocturnal elevations of blood pressure or a disruption of the normal diurnal blood pressure pattern? If so, counseling regarding salt intake, dynamic exercise, and maintenance/reaching of ideal body weight is in order.

In 1988, Wilson et al. obtained 24-hour ABP monitoring data on 77 children with one or two hypertensive parents and compared them to data from 101 controls.[189] They found that there were significant differences in diastolic blood pressure during school hours; children of hypertensive parent(s) had higher diastolic blood pressure. The authors speculated that the school hours contained stressful stimuli, such as tests, quizzes, speeches before the class, social interactions, etc. The children did not differ

with respect to systolic blood pressure or diastolic blood pressure on casual measurements, only those obtained by 24-hour ABP monitoring. Thus, the children of hypertensive parent(s) had an increased blood pressure load compared to their counterparts with normotensive parents. This additional load may lead to premature persistent elevations of blood pressure and early-onset essential hypertension.

An extensive study by Hornsby et al. determined that there is a significant incidence of white coat hypertension in children aged 5 to 15 years.[190] They studied 159 children with a positive family history of essential hypertension; 39 had elevated systolic blood pressure on casual measurement, and 120 were volunteers from the public school system. The authors found that 44% (n=15) of the 34 children with elevated casual blood pressure had normal pressures during 24-hour ABP monitoring. These children would have been classified as being hypertensive were it not for the 24-hour ABP monitoring. The cost and invasiveness of an evaluation for essential hypertension far exceed the cost of 24-hour ABP monitoring. Of note is that a high percentage of the hypertensives and white coat hypertensives in Hornsby's study were overweight; 24-hour ABP monitoring would be especially important in the evaluation of an obese child with elevated casual blood pressure.

The 24-hour ABP monitoring patterns in hypertensive adolescents have been described by two investigative groups; Garrett et al. and Fixler et al.[191,192] The former study was performed on ten hypertensive patients with excessive systolic blood pressure response to dynamic exercise and ten controls. The resting blood pressure in the hypertensives was 138/87 and 124/78 mm Hg in the controls. None of the subjects was on an antihypertensive medication. In hypertensives, the normal circadian blood pressure pattern was not seen. The hypertensives had more blood pressure variability ($p<.05$) than the controls, especially during sleep when the controls significantly reduced their blood pressure variability. Garrett stated that ABP monitoring should be able to define an at-risk population. They speculated that: 1) exaggerated catecholamine secretion or a lack of feedback inhibition could explain the blood pressure findings; 2) the 24-hour ABP monitoring profile may serve as a marker for early adult-onset essential hypertension.

The study by Fixler et al. described the investigation of 24-hour ABP monitoring in 10 hypertensive and ten control adolescent males.[192] The hypertensives were not receiving pharmacologic therapy. As in Hornsby's study described above, the hypertensive adolescents were heavier than the controls. Both groups showed diurnal variation of systolic blood pressure. There was a persistent systolic blood pressure difference between hypertensives and normotensives, which was greatest in the afternoon hours when a normal diurnal blood pressure peak occurs. There was a disproportionate percentage of the hypertensive boys who had elevated systolic blood pressure during school hours. Ambulatory blood pressure monitoring in the natural environment provided data showing physiologic responses to the children's workplace. The investigators suggested that the clinician evaluating blood pressure elevations in children should do 24-hour ABP monitoring while the child attends school, rather than during a weekend or school holiday.

5.5 Ambulatory Blood Pressure Monitoring in Antihypertensive Therapy

The use of ABP monitoring in judging the efficacy of hypertension therapy has become routine. To date, we are not aware of any prospective study which has assessed pharmacologic or nonpharmacologic interventions of hypertension therapy in children and adolescents. As pediatricians and family physicians become more conscious of blood pressure elevations, especially in adolescents, the use of ABP monitoring should become as routine as it is in adult therapy.

6.0 AMBULATORY BLOOD PRESSURE MONITORING IN PREGNANCY

Throughout the developed world, pre-eclampsia and eclampsia are the most significant cause of maternal mortality.[193-195] They are also important causes of morbidity to both the mother and fetus. Perinatal mortality increases with pre-eclampsia, especially when it is associated with proteinuria. It is particularly high in eclampsia, the reported incidence ranging between 13 and 64%.[196,197]

The incidence of hypertension arising in pregnancy varies according to the definition and to parity, age, and underlying medical disease, but the incidence is typically reported at more than 10% of pregnant women. Fetal and maternal morbidity and mortality are higher in pre-eclampsia than in chronic hypertension that has predated the pregnancy. Hypertension can be caused by the pregnancy itself, or may exist from before conception (being unrelated to the pregnancy), and, rarely, may present for the first time in pregnancy. Pre-eclampsia is a disorder of the second half of pregnancy which regresses after delivery. The cause is unknown but is related to an intrauterine/placental problem. The maternal neurological, cardiovascular, renal, coagulation, and hepatic systems can all be affected. Pre-eclampsia is the most important cause of intrauterine growth retardation when no malformation exists in the fetus.[198] This is due to involvement of the utero-placental unit in the disease process.

Hypertension is a secondary sign of pre-eclampsia, but is important as it is an early indication of the disease and a key diagnostic sign. It can also be a cause of morbidity in severe disease through direct arterial injury. Other clinical indications of the disease, such as symptoms of headache, epigastric pain, and visual disturbance, or the neurological manifestations, such as hyper-reflexia and clonus, tend to be later consequences of the disease.

The diagnosis of hypertension has important implications for the management and prognosis of both the mother and her fetus, and is dependant on the accurate measurement of blood pressure. Current definitions of blood pressure in pregnancy are based on absolute thresholds, suggesting precision where none exists. This section will describe the blood pressure changes in pregnancy, the difficulties encountered using conventional sphygmomanometry, and the potential advantages of 24-hour ambulatory blood pressure (ABP) monitoring in pregnancy.

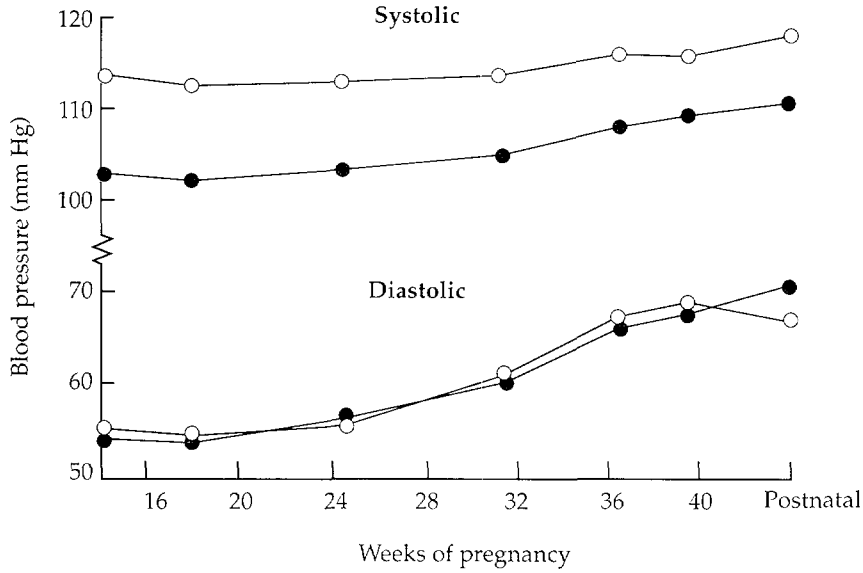
6.1 Physiology

Blood pressure is the product of cardiac output and total peripheral resistance. The cardiac output increases by about 40% in pregnancy to maintain adequate oxygenation of the uterus and fetus, as well as to support the increased metabolic rate of the mother. At least two-thirds of this increase will have occurred in the first 12 weeks of gestation. This increase is primarily achieved through a larger stroke volume, but there is also a 10% increase in heart rate.

In normal pregnancy blood pressure falls in the second trimester. In the face of increased cardiac output, this is achieved by a marked fall in peripheral vascular resistance. Cardiac output increases early in pregnancy, but the blood pressure does not rise. The low resistance shunt of the pregnant uterus is not sufficient in the first trimester to account for this increase in cardiac output. The decrease in peripheral resistance is achieved through active vasodilation. In the past this was thought to be estrogen mediated, though now it is thought more likely that local mechanisms, such as prostacyclin and endothelium-derived relaxing factor (EDRF), are the major contributing factors. There is a refractoriness to the pressor effects of angiotensin infusion as compared with the nonpregnant state.[199]

Blood pressure increases again in the third trimester to normal prepregnancy levels. Figure 6.1 demonstrates changes in the office blood pressure readings (taken lying and sitting in 226 primigravid women) that occur during normal pregnancy, and at six weeks postpartum.

Figure 6.1 — Changes in the office blood pressure readings (taken lying and sitting in 226 primigravid women) that occur during normal pregnancy, and at six weeks postpartum: lying (○), sitting (●).



6.2 *Blood Pressure Measurement*

6.2.1 Difficulties with Conventional Sphygmomanometry

Conventional sphygmomanometry involves an observer, a sphygmomanometer, and a stethoscope, all which may have inherent sources of error. These errors are confounded by the fact that blood pressure can vary considerably throughout the day, and a single (or few) readings can be unrepresentative of a person's true blood pressure. Conventional sphygmomanometry is also labor intensive if anything more than a few readings are required.

6.2.2 Blood Pressure Variability

Variation in blood pressure recordings can be due to either errors obtained in the measurement of the blood pressure, or to the circumstance of the individual.

6.2.2.1 Within Patient Variation

Systematic variation in blood pressure is defined as a constant and recurrent biological phenomenon and is the variation that occurs between different races, age groups, and sexes (women have lower blood pressure than men until after the age of 45).[200] It also includes the blood pressure change according to the time of day. There is a circadian rhythm of blood pressure which is maintained in normal pregnancy.[201] Highest readings are seen during the afternoon and early evening, and the lowest during sleep, between midnight and 4:00 a.m.[202] These variations seem to be unaffected by uncomplicated chronic hypertension.[201,203,204]

The random variations of blood pressure that occur in an individual and between individuals are most likely to result in sampling errors with conventional sphygmomanometry. Blood pressure is dependant on a number of variables which are themselves continually fluctuating. They include heart rate, stroke volume, and peripheral resistance, which in turn are influenced by many other factors depending on the physical or emotional state of the individual. It is, therefore, unlikely that a single or few random blood pressure recordings would accurately reflect an individual's true blood pressure.

Random variation is largely influenced by external phenomena such as activity and anxiety. Even meals, smoking, temperature, and the season of the year will influence blood pressure.[205] Blood pressure measured intra-arterially fluctuates markedly in women during minor stimulation such as conversation.[206] Therefore, obtaining an accurate basal blood pressure, by eliminating all significant stimuli, is likely to be difficult when blood pressure changes are provoked by an innocuous stimulus such as conversation. These random changes impede the ability of conventional sphygmomanometry to reflect the true blood pressure of an individual, in so far as a single or few readings may not reflect this appropriately.

The anxiety caused by the measurement itself can influence blood pressure by what is known as defense reaction.[207] This may explain why some women are suscep-

tible to higher readings when attending hospital clinics or their obstetrician. Whether this is a significant problem causing unnecessary investigation or followup, or even inappropriate intervention, is difficult to quantify. Clinic blood pressure readings were found to be significantly different from home readings in nearly half of pregnant women; and in 85% of these, the readings were found to be lower at home.[208] There are no comparisons between pregnant and nonpregnant individuals as to the degree that this defense reaction causes blood pressure to change, but in view of the immediate implications to the mother and to her fetus (admission to hospital, premature delivery), it seems probable that the influence of anxiety and stress are likely to be greater in a pregnant patient.

Of course, most epidemiological studies relating outcome to blood pressure are based on clinic measurements. But maybe this is why blood pressure alone is such a poor predictor of outcome in pregnancy.

6.2.2.2 Variability Due to Measurement or Observer Errors

With conventional sphygmomanometry, variation due to measurement can either occur because of errors in the instrument or in the observer.

A poorly functioning manometer that is incorrectly calibrated can lead to measurement error. With a mercury column, the meniscus should be clearly visualized and should settle at 0 before inflation. Oxidized mercury within the glass tubing can obscure vision. A blocked air vent, dirt within the tube, or a cracked tube can all lead to inaccurate calibration. Aneroid manometers will lose accuracy over time and need to be checked against a standardized mercury column manometer.

Too jerky or rapid deflation will under- and overestimate the systolic and diastolic blood pressure, respectively. A slow deflation may cause sufficient discomfort to raise the blood pressure.[205] The inflation-deflation device must be able to reach 200 mm Hg, or 40 mm Hg above the estimated systolic blood pressure after 3 to 5 seconds of rapid inflation. A smooth deflation of 2 to 3 mm Hg per second using the control release valve should be achieved.

Both the length and width of the bladder within the occluding cuff are important. Incorrect cuff size can lead to errors. If the cuff is too small, the cuff pressure will not be fully transmitted to the artery. A standard cuff with 12 x 23 cm bladder over-estimated the diastolic blood pressure by 5 to 10 mm Hg and the systolic by 7 to 13 mm Hg in obese patients.[209] It is recommended that the bladder length be at least 80% and the width 40% of the circumference measured around the middle of the upper arm.[205] A large cuff in a thin patient only underestimates the diastolic blood pressure by 3 to 5 mm Hg.

The stethoscope can influence the quality of sound that the observer must interpret. As the length of tubing increases, sound transmission will be poorer. This may be of importance in pregnancy where it is necessary to detect the Korotkoff phase IV sound which is identified by muffling of sound which has a soft quality.

Many factors will determine the ability of an individual to accurately measure blood pressure using conventional sphygmomanometry. They include concentration, reaction time, hearing, and visual acuity, all which are difficult to standardize. Poor technique involving such aspects as posture of the patient, position of the manometer, rate of cuff deflation, and interpretation of the sounds can result in errors dependant on the individual observer.

The sphygmomanometer cuff should be approximately level with the heart to avoid the hydrostatic effect of a column of blood above or below the heart, which correspondingly increases or decreases the recorded blood pressure. In pregnancy, blood pressure measurements are frequently made with the woman lying in the left lateral position, and these errors will apply when measurements are taken in the upper and lower arms, when the arm is not level with the heart.

The posture of a pregnant woman can affect the blood pressure, though in clinical practice a number of different positions are used to record pressure.[210] In pregnancy, particularly with advanced gestation, lying supine can cause profound drops in blood pressure due to obstruction of the inferior vena cava. Blood pressure seems to be lowest when measured in the left lateral position, using the uppermost arm, and increases on sitting or becoming erect.[211]

When recording a blood pressure, the observer must coordinate the visual sign of a falling column of mercury with the acoustic signal of the intermittent Korotkoff sounds. The rate of fall and the pulse rate will determine the degree of estimation that is made. The observer will take the nearest round figure of the sound change, and this can vary according to digit preference. A recent survey of the practices of obstetricians and midwives in a district general hospital showed that nearly 25% rounded blood pressure readings to the nearest 10 mm Hg.[210] This is contrary to current recommendations that blood pressure be estimated to the nearest 2 mm Hg.[212] When the inherent inaccuracies of indirect blood pressure measurement compared with intra-arterial pressure are considered and are added to the worst observer practices (measuring blood pressure to the nearest 10 mm Hg), a diastolic measurement of 90 mm Hg may be as high as 128 mm Hg or as low as 74 mm Hg.[213] Management at the extremes of this range would be entirely different.

Another way in which an observer can bias a reading is by ignoring blood pressures in which action may be necessary, and only note further readings which are below this threshold. This is known as threshold avoidance.

In some women there exists a silent zone between the systolic and diastolic points, known as the auscultatory gap. The cuff may not be sufficiently inflated, particularly in hypertensive individuals with a high systolic blood pressure, and the returning sounds following this gap may be mistaken for the systolic point. For this reason the cuff should be initially inflated while palpating a distal artery (e.g., brachial or radial) and identifying an estimated pressure of systolic blood pressure prior to auscultating.

All these areas of potential error contribute to the inaccuracies of conventional sphygmomanometry, particularly when isolated readings are taken, as is common in clinical practice.

6.2.3 Korotkoff Phases IV and V in Pregnancy

The British Hypertension Society recommends the use of the fourth Korotkoff sound (phase IV) to signify diastolic blood pressure in pregnancy. The fifth Korotkoff sound (phase V), represented by the disappearance of sounds, is occasionally not audible, i.e., sounds are heard down to 0 pressure. This is a consequence of the reduced peripheral resistance that occurs in pregnancy. In spite of this, phase V is likely to be more accurate as it overestimates true intra-arterial pressure less than does phase IV.[213] Phase IV should perhaps only be used in those women with no audible phase V, but as this may be confusing, the muffling remains the recommended identifying point for diastolic blood pressure in pregnancy.[205] However, the fifth phase diastolic end-point is still used by a large proportion of clinicians and one of the major problems with conventional sphygmomanometry has been the difficulty in standardizing the measurement.[210]

6.3 Ambulatory Blood Pressure Measurements

6.3.1 Methods of Ambulatory Measurement and Retail Devices in Pregnancy

The diagnosis of hypertension in pregnancy is often made from occasional readings that are subject to bias, as well as to measurement and sampling errors. It has been suggested that the use of 24-hour ABP monitoring in pregnancy may eliminate many of these inaccuracies.[214] Self-monitoring of blood pressure has been advocated as a method of monitoring blood pressure away from the clinical setting, but has the potential for increasing biased data, and requires patient motivation. The readings are obtained when clinicians are not present to interpret their significance, and this may lead to anxiety when high readings are recorded in the home environment.

Portable, intra-arterial direct surveillance systems have been used to monitor blood pressure on a 24-hour basis in nonpregnant individuals. Although this has provided accurate, continuous blood pressure recordings, the technique is invasive, cumbersome, and impractical for routine clinical practice. Clinical management must rely on indirect measurement of blood pressure. Noninvasive portable devices providing ambulatory monitoring are now being used more widely, and this technique is gaining acceptance as a useful procedure in clinical practice.[207,215]

A number of centers are currently investigating the use of ABP monitoring in pregnancy, and provisional data suggest that this form of monitoring is very acceptable to the patients.[214]

6.3.2 Validation for Use in Pregnancy

There are at least 15 different brands of monitors currently available which take intermittent indirect blood pressure measurements via a cuff placed on the upper arm.[216] The first two ABP monitors to be validated for use in pregnancy were the Takeda-2420 and the SpaceLabs Medical 90207. Experience with these monitors is far greater than with any others to date in pregnancy.

The Takeda TM-2420 is a lightweight ABP monitor (390 grams), that can be programmed into four different measurement periods within a 24-hour period. Eight inflation intervals are possible (off, 1, 3, 5, 10, 15, 30, or 60 minutes), and 300 measurements can be taken on a single battery charge. It has a warning buzzer that can be inactivated. Measurement errors are identified by code numbers, and an automatic repeat occurs after 5 seconds if an inflation fails to record a reading. Measurement results can be displayed or disabled as required. Results can be printed in a numeric or graphic format using the accompanying TM-2020 decoder which contains a thermal printer, and can be transmitted to a computer for data storage and analysis.

The TM-2420 uses the Korotkoff method to measure blood pressure and requires accurate cuff placement with positioning of a lower microphone over the brachial pulse. The instruction manual recommends that the cuff be taped for optimal readings. For this reason, it is generally not feasible for the cuff to be removed and reapplied by the patient. This is a distinct disadvantage as removal is often desired for bathing or changing clothes.

To validate the Takeda TM-2420 in pregnancy, procedures recommended by the Association for the Advancement of Medical Instrumentation (AAMI) for electronic or automated sphygmomanometers were used.[217,218] The monitor's measurements were compared with those taken simultaneously by two trained observers using a random zero sphygmomanometer. Three measurements were made in each of 30 pregnant women. The mean difference between the monitor and the average of the observer measurements are shown in Table 6.1. The accuracy stipulated by AAMI were met for the systolic blood pressure and phase V, therefore, the TM-2420 provides reliable estimates of systolic and Korotkoff phase V diastolic blood pressures in pregnancy.

Table 6.1 – Mean Difference Between the TM-2420 Monitor and Average of Observer Measurements

	Mean Difference (Standard Deviation)
Systolic Blood Pressure:	0.53 (2.7) mm Hg
Diastolic Blood Pressure (phase IV):	5.40 (5.3) mm Hg
Diastolic Blood Pressure (phase V):	0.87 (3.7) mm Hg

It must be pointed out that this validation procedure used the Hawksley random zero sphygmomanometer. It has been demonstrated that this instrument systematically underestimates blood pressure. It gives a reading on average 3.5 mm Hg lower than a standard mercury sphygmomanometer for systolic blood pressure and 7.5 mm Hg lower for diastolic blood pressure.[219] A recent publication in the British Medical Journal concluded that the use of the Hawksley instrument as a blood pressure measuring device cannot be justified.[220] It should not be used as a standard in assessing the perfor-

mance of automated devices, as it gives an advantage to the instruments with a similar bias as the Hawksley and vice versa.

A further concern regarding the validation of the Takeda TM-2420 is its frequent upgrading by the manufacturer. The validation procedure in pregnancy was performed on the fourth version of the TM-2420, though this has been upgraded three times since.[218] The latest device, therefore, should undergo further validation before its use can be recommended in pregnancy.

The SpaceLabs Medical 90207 monitor weighs 346 grams and is more compact than the Takeda device. It has many features similar to the TM-2420. There are 12 independently programmable periods, with a six- to 60-minute inflation frequency. Though the TM-2420 has the advantage of automatic recordings at one-, three-, or five-minute intervals, outside this range the SpaceLabs Medical 90207 provides a greater frequency choice. Two hundred and forty readings can be stored in memory, and it can be programmed for many days. Warning inflation beeps (which can be disabled), error codes, and automatic repeat (1 minute) should a measurement fail, make it similar to the Takeda monitor. A useful feature is the beeps that inform the patient that it has failed to obtain a reading, so that if this is patient-related (e.g., movement) the individual can adjust their activity accordingly. Rechargeable batteries can be used but need to be changed between patients. This is not as convenient as charging the Takeda in its decorder, but has the added advantage of allowing the monitor to be reused immediately. Data is easily stored on a personal computer, and a programmable software package allows appropriate manipulation of the data for analysis, giving the advantage of being upgradeable without changing hardware.

The SpaceLabs Medical 90207 uses the oscillometric technique for measuring blood pressure. This does not require precise cuff placement as there is no need for a microphone or sensor in the cuff. Oscillatory pressure changes can be noted from above systole, gradually increasing as the pressure drops, until they reach a maximum at the mean blood pressure. They then decrease until below the diastolic pressure. Functions of the changes in amplitude of these pressure waves are used to determine the systolic and diastolic blood pressures.

A more extensive validation of the SpaceLabs Medical 90207 has been done (compared to the Takeda validation) for use in pregnancy.[221] The protocol of the British Hypertension Society (BHS) for the evaluation of automated and semiautomated blood pressure measuring devices with special reference to ambulatory systems was used, with suitable modifications for pregnancy. The BHS protocol addresses certain deficiencies that are inherent in the AAMI standard. These include aspects of evaluation regarding interdevice variability, ambulatory assessment, and patient acceptability. The AAMI standard also has problems with statistical methodology.[222] During the 90207 device validation, 98 subjects each had four readings taken sequentially, by one of two trained observers, which were compared with the monitor's readings.

The mean difference between observer and device for systolic blood pressure was 3 mm Hg [standard deviation (SD) 4]. For diastolic blood pressure the difference was 5 mm Hg (SD 6) for phase IV (muffling of Korotkoff sound), and 4 mm Hg (SD 4) for phase V (disappearance of Korotkoff sound); see Table 6.2. According to the BHS grading criteria (Table 6.3) the device reached a 'B' grading for the systolic blood pressure. A 'B' grading was also reached for the diastolic blood pressure (phase V), while a grade 'C' was reached for the diastolic blood pressure (phase IV). The accuracy criteria stipulated by AAMI also were met for both systolic blood pressure and diastolic blood pressure (phase IV and V).

Table 6.2 – Validation for paired measurements (n=294) showing the mean SBP and DBP for observer and device as well as the mean of the absolute value of the differences

		Mean (SD)	Difference (SD) (Absolute Values)	Readings % (mm Hg diff.)		
				< 5	< 10	< 15
SBP	Observer	124 (13)	3 (4)	78	95	99
	Device	124 (12)				
DBP	Phase IV	81 (12)	5 (6)	62	86	97
	Phase V	78 (13)	4 (4)	74	92	98
	Device	76 (11)				

(SD=standard deviation)

Table 6.3 – Grading Criteria Based on Cumulative Percentage of Readings (British Hypertension Society Protocol for Blood Pressure Measuring Devices)

Grade	Difference Between Standard and Test Device (mm Hg) ≤ 5	≤ 10	≤ 15
A	80	90	95
B	65	85	95
C	45	75	90
D	Worse than C	Worse than C	Worse than C
(For SpaceLabs Medical 90207 Monitor, 98 subjects, 294 readings)			
SBP	78	95	99
DBP phase IV	62	86	97
DBP phase V	74	92	98

Figure 6.2 shows the Bland Altman plot of the pressure differences (observer minus device) against the systolic blood pressure (calculated as the mean of the device and the observer's reading).[222] Lines have been drawn to demonstrate the points within 5, 10, and 15 mm Hg difference. The percentage of points within these lines determines the BHS grade (Table 6.3). Figures 6.3 and 6.4 show similar plots of the pressure differences against diastolic blood pressure, phase IV and V respectively.

Figure 6.2 — Bland Altman plot of the pressure differences (observer minus device) against the systolic blood pressure (calculated as the mean of the device and the observer's reading).

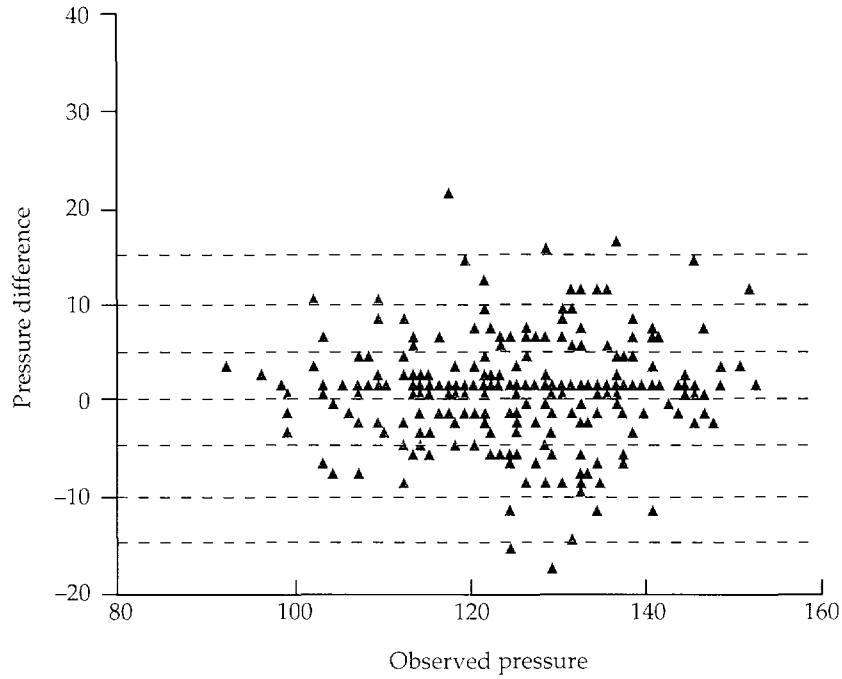


Figure 6.3 — Similar plots of the pressure differences against diastolic blood pressure for phase IV.

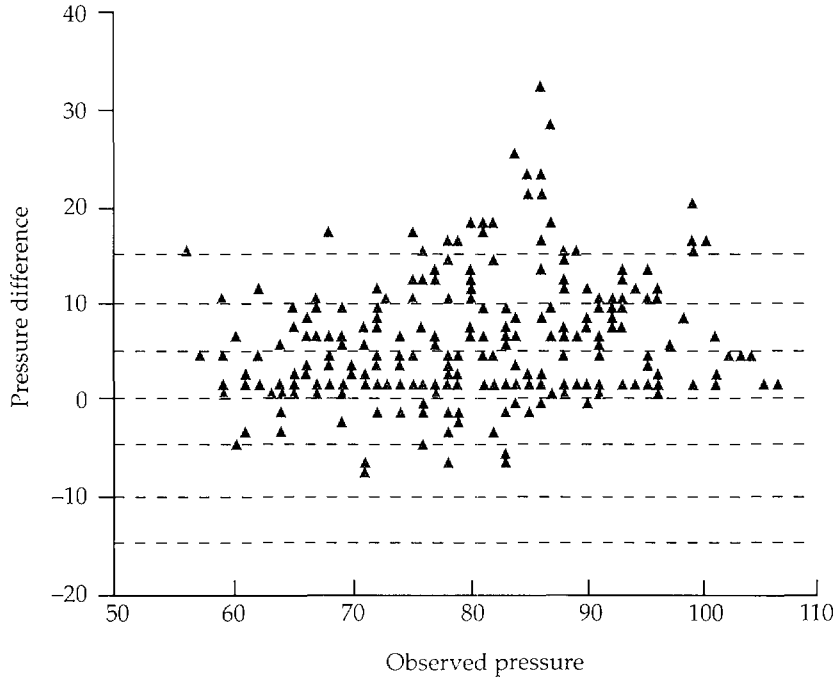
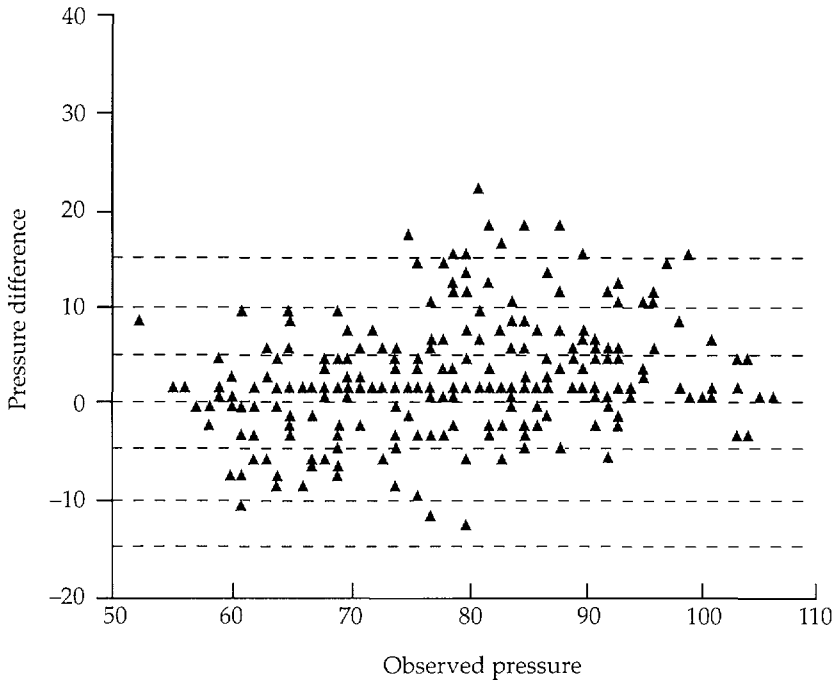


Figure 6.4 — Similar plots of the pressure differences against diastolic blood pressure for phase V.



When compared to trained observers, the SpaceLabs Medical 90207 is accurate in determining both the systolic and diastolic blood pressure for clinical purposes as judged by the BHS protocol in pregnancy.

In this study, the observers' diastolic blood pressure readings for phase IV and V were both higher than the SpaceLabs Medical monitor. A comparison of intra-arterial and sphygmomanometer pressure measurements in pregnancy suggests that the use of the phase IV Korotkoff sound overestimates diastolic pressure by 11 mm Hg, whereas the use of phase V overestimates by 7 mm Hg.[223] This suggests that for diastolic blood pressure the device gives a figure that is nearer intra-arterial pressure than the figure given by an observer for phase V; i.e., the SpaceLabs Medical 90207 device is more accurate than conventional sphygmomanometry for the measurement of diastolic blood pressure.

However, all data relating prognosis to blood pressure come from conventional sphygmomanometry. Therefore, future use of ambulatory monitoring will need to establish normal values for ABP readings and the relationship of abnormal values to prognosis.

6.3.3 Normal Ambulatory Values in Pregnancy

Normal values of 24-hour ABP measurement in a primigravid population have been determined.[224] One hundred and six consecutive primigravid women who did not

have a history of previous hypertension, renal or cardiovascular disease, or diabetes mellitus were studied. Twenty-four-hour ABP monitoring was performed on five separate gestational periods on each subject (9 to 16, 18 to 24, 26 to 32, and 33 to 40 weeks, as well as 6 weeks postpartum) using the SpaceLabs Medical 90207 ABP monitor. The device was programmed to obtain readings every 30 minutes during the 24-hour period, and was fitted between 9:00 a.m. and 10:00 a.m. Daytime was defined as 10:00 a.m. to 10:59 p.m. and nighttime, 1:00 a.m. to 6:59 a.m. As long as the 24-hour recording had at least 15 readings it was considered acceptable. One clinic blood pressure was taken when the woman was recruited for 24-hour ABP monitoring. The fourth Korotkoff sound was used for the diastolic blood pressure. Table 6.4 shows the mean (and standard deviation), median, and 95th percentiles for the day, night, and clinic blood pressure measurement for both systolic blood pressure and diastolic blood pressure in each of the five measurement periods. The average number of recordings obtained was 23 during the day and 11 at night.

Ninety-eight out of the 106 women completed the study. Six dropped out of the study, and two did not fulfill the required number of recordings to be included. Four women delivered prematurely and, therefore, did not complete the last 24-hour ABP measurement. No one withdrew because they found the procedure unacceptable.

As compared with the first 24-hour ABP measurement, the systolic blood pressure did not rise significantly until the 33 to 40 week period. The postpartum systolic blood pressure was not significantly higher during the day but was at night. Diastolic blood pressure was lower at 18 to 24 weeks (for both the night and day) and increased at 33 to 40 weeks in a similar fashion to the systolic blood pressure. Diastolic blood pressure was raised at 6 weeks postpartum compared to the first ABP measurement.

Table 6.4 also shows the mean (and standard deviation), median, and 95th percentile blood pressures for systolic and diastolic blood pressures in the five gestational periods. The daytime ABP and clinic blood pressures were significantly different up to 33 weeks for both systolic (-8 mm Hg) and diastolic (-9 mm Hg) blood pressures. After 33 weeks there was no significant difference between clinic and ambulatory readings.

Within the study, four women developed proteinuric hypertension, and three of these had elevated nocturnal systolic blood pressures between 18 and 24 weeks. This occurred between 13 and 21 weeks prior to clinical detection. This loss of nocturnal dip was confined to these three women.

6.3.4 Application to Potentially Pathological Pregnancy

6.3.4.1 Advantages of Outpatient Monitoring

A single blood pressure recording may only reflect the blood pressure at a given moment and may be highly unrepresentative of the average blood pressure. It is, therefore, generally accepted that isolated readings that are elevated should be verified by repeating measurements 4 to 6 hours apart.[225] This can be very difficult or inconvenient, involving time spent in clinics, or offices, or even admission to a hospital, which involves nursing time as well as expense of in-patient management.

Measuring blood pressure with an automated ABP device will enable the patient to return home and continue her daily routine. This should lead to significant cost benefits by reducing bed occupancy rates, and by allowing trained staff to perform other duties.

Table 6.4 – Twenty-Four-Hour Ambulatory Blood Pressure Measurements (mm Hg) in 100 Primigravid Women

Weeks Gestation (No. Women)	9 to 16 (98)	18 to 24 (98)	26 to 32 (98)	33 to 44 (94)	6 weeks post partum (98)
Daytime ABP					
SBP:					
Mean (SD)	115(8)	115(8)	116(9)	119(9)	118(9)
Median	115	113	115	119	116
95th percentile	128	128	132	134	132
DBP:					
Mean (SD)	70(7)	69(6)	70(7)	74(7)	76(7)
Median	70	68	70	72	75
95th percentile	82	80	85	86	87
Night-time ABP					
SBP:					
Mean (SD)	100(7)	99(8)	101(8)	106(8)	104(10)
Median	99	98	100	106	102
95th percentile	114	113	115	119	118
DBP:					
Mean (SD)	55(5)	54(6)	55(6)	58(7)	59(8)
Median	54	53	55	58	58
95th percentile	65	64	67	71	71
Clinic BP:					
SBP:					
Mean (SD)	121(10)	124(10)	123(10)	119(10)	117(8)
Median	120	120	122	120	116
95th percentile	140	140	138	135	130

6.3.4.2 Decision to Monitor, Admit or Induce Labor

Many of the errors associated with conventional sphygmomanometry can be avoided by using automated ABP devices. There are no observer errors, and many more readings taken in the patient's own environment should improve characterization of an individual's blood pressure. Those pregnant women who genuinely have raised blood pressure can be identified and patients who are susceptible to white coat hypertension excluded from unnecessary investigation or intervention.

Figure 6.5 — Blood pressure data taken from the ambulatory 24-hour recordings of a woman diagnosed as hypertensive by conventional sphygmomanometry at 19 weeks gestation.

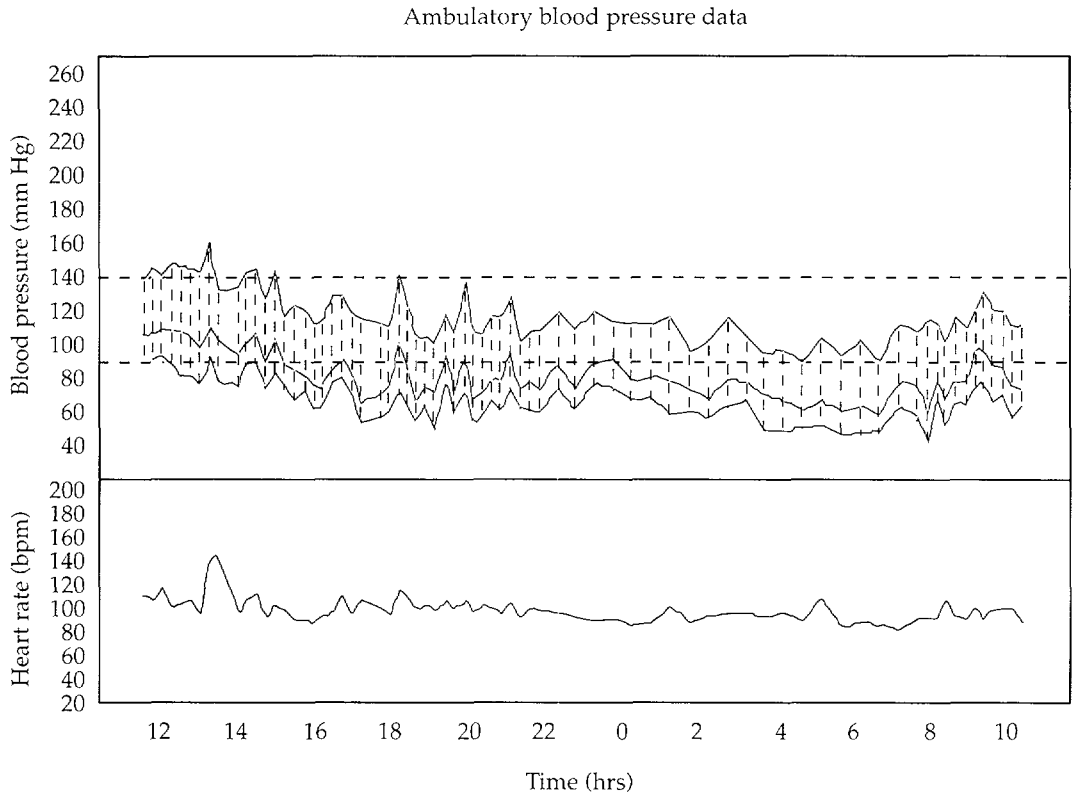


Figure 6.5 shows blood pressure data taken from the ambulatory 24-hour recordings of a woman diagnosed as hypertensive by conventional sphygmomanometry at 19 weeks gestation. The conventional readings immediately prior to this 24-hour ABP measurement were 160/90 mm Hg on two occasions. The results of the ABP measurement were blinded from her attending physicians as part of a study into the value of 24-hour ABP monitoring. This clearly demonstrates a tendency to hypertension only while at the hospital. The daytime average ABP (10:00 a.m. until 10:59 p.m.) was only 123/71 mm Hg. Further management based on the conventional blood pressure measurements included repeated visits to a clinic. Serial investigations of liver, renal, and clotting function were normal, as was a 24-hour collection of urine for vanilmandelic acid.

The subsequent average conventional blood pressure recordings between 19 and 34 weeks gestation taken at clinic visits or within the hospital (20 measurements) was 155/90 mm Hg. Two further 24-hour ABP measurements at 29 and 34 weeks demonstrated identical patterns to the first ABP measurement (high initial blood pressure readings while at the hospital) and the average daytime blood pressures during ABP monitoring were even lower than at 19 weeks gestation.

The use of 24-hour ABP monitoring should improve the management of women who have been found to have high clinic blood pressure by identifying those who genuinely have raised blood pressure. Unnecessary admissions, or even intervention such as induction of labor, could be avoided. Readings taken frequently in the patient's own environment most closely reflect the level of blood pressure which af-

fects the individual on a day-to-day basis and, therefore, are more likely to identify the patient with a pathological condition.

Further studies are needed to investigate whether this improved characterization of blood pressure, involving the larger and potentially more accurate data set of 24-hour ABP recordings, relates more closely to prognosis than does conventional sphygmomanometry.

6.3.4.3 Decision to Treat

There is a natural reluctance for women to take medication during pregnancy for fear of adverse effects on the fetus. When medication is required, an obstetrician will tend to use tried and tested drugs that have a good safety record. Many modern and effective antihypertensive drugs such as beta-blockers and angiotensin converting enzyme inhibitors are known to have adverse effects on the fetus and, therefore, are not prescribed.[226,227] Older antihypertensive drugs such as methyldopa, which are more likely to cause unpleasant side effects in the mother, are more frequently used. For these reasons it is particularly desirable in pregnancy to exclude those women from treatment who have white coat hypertension.

Antihypertensive medications have actually been withheld following self-monitoring of blood pressure at home.[208] Pregnant women with chronic hypertension who had clinic blood pressure measurements which were consistently in a borderline range had lower average blood pressure recordings at home; treatment was, therefore, not started. Twenty-four-hour ABP monitoring has been used in nonpregnant patients to preclude treatment in individuals with borderline conventional blood pressure who are normotensive during ABP monitoring. Its use in pregnancy is likely to be beneficial by more accurate identification of those women with severe chronic hypertension who should be treated from early pregnancy.

6.3.4.4 Monitor Treatment/Improve Compliance

Once the decision to treat has been made, an optimum dosing regimen should be identified. Twenty-four-hour ABP monitoring can be used to monitor the effects of antihypertensive therapy and allow accurate adjustment of dose. This may improve compliance in some women. Side effects can be minimized by obtaining the lowest effective dose. In others, compliance may also be improved by demonstrating raised blood pressure throughout the day, including when at home, as some women believe their blood pressure is only raised when they are in the clinic and are reluctant to take drugs in pregnancy. There is also some evidence that in pre-eclampsia, blood pressure may be high at night when not normally recorded, in spite of good control during the day.[228] Twenty-four-hour ABP monitoring allows assessment of the nocturnal blood pressure and may aid in directing dosage and timing of therapy.

6.3.4.5 Monitor At-Risk Pregnancy

Pre-eclampsia is more likely to occur in women who are hypertensive, have had previous severe pre-eclampsia, or who have certain medical disorders such as systemic lupus erythematosus or underlying renal disease. Though it is impractical to screen all pregnancies using the potentially more accurate 24-hour ABP monitoring, these at-

risk women may benefit from longitudinal 24-hour ABP monitoring assessments in order to allow early identification of pre-eclampsia.

6.3.4.6 Other Diagnostic Uses

Pre-eclampsia is a multisystem disorder, and on occasions may be present with other clinical manifestations when there is a normal clinic blood pressure. Symptoms associated with pre-eclampsia such as headache, epigastric pain, or nausea and vomiting can be due to many other causes in pregnancy. Similarly, proteinuria can be a sign of urinary tract infection, which is not uncommon in pregnancy. Twenty-four-hour ABP monitoring may be a useful additional investigation if there is suspicion of pre-eclampsia with normal clinic blood pressure readings.

Pheochromocytoma is associated with a poor prognosis in pregnancy and maternal mortality rates have been noted as high as 50%.[229] It is important to identify this rare condition as the mortality can be reduced to zero with alpha adrenergic blockade. All women who are found to have severe hypertension in early pregnancy should be screened for pheochromocytoma. Because it can be associated with episodic hypertension, 24-hour ABP monitoring may also assist in detection.

6.3.5 Predicting Severity or Outcome of Hypertensive Disease in Pregnancy

One of the advantages of 24-hour ABP monitoring is the ability to measure diurnal blood pressure variation. There is a fall in nocturnal blood pressure associated with sleep; in normal pregnancy this fall is similar to nonpregnant individuals.[201] When pregnancy is complicated by essential hypertension there remains a normal diurnal pattern.[201,228] In pre-eclampsia, a blunting of the nocturnal fall has been demonstrated. In cases of severe pre-eclampsia with renal involvement, a reversal of the diurnal blood pressure rhythm can be seen.[203] These observations have not yet been evaluated on a large number of patients but may provide a useful sign to monitor disease severity and aid in the timing of intervention.

Loss of the nocturnal dip in early pregnancy may have a predictive value for pre-eclampsia.[214] Out of 98 normal primigravid women who had serial ABP measurements, four had raised nocturnal blood pressure readings between 18 and 24 weeks, three of whom developed proteinuric hypertension. No other women developed proteinuric hypertension, but three of the remaining 94 developed nonproteinuric hypertension. The value of this sign is currently being evaluated in Dublin with a larger series.

6.4 Conclusions

Twenty-four-hour ABP monitoring is likely to be of significant benefit in prenatal care. It will provide more accurate data on which to base clinical decisions by overcoming sampling and measurement errors associated with conventional blood pressure determination. The cost of equipment can be justified by the potential savings of outpatient monitoring and improved assessment resulting in fewer admissions.

There may be some benefit in the ability of 24-hour ABP monitoring to determine nocturnal hypertension as a possible indicator of pre-eclampsia.

Further studies will need to establish the relationship between 24-hour ABP recordings and prognosis in pregnancy, and will need to include the significance of the 24-hour profile. Abnormal ABP values should be defined by relating values to outcome, and should theoretically be more accurate than the current definition of hypertension in pregnancy based on conventional readings.

7.0 AMBULATORY MONITORING FOR THE EVALUATION OF ANTIHYPERTENSIVE TREATMENT

The effectiveness of antihypertensive treatment, whether pharmacological or nonpharmacological, is traditionally evaluated by blood pressure measurements made in the clinic at regular intervals. Ambulatory monitoring and patient self-monitoring offer a number of advantages, both from the point of view of the researcher attempting to assess a new form of treatment and the clinician. The basis of this superiority rests on the unreliability of the clinic measurements, not only because they may be unrepresentative of blood pressure levels at other times, but also because of their relatively poor reproducibility from one occasion to another. Ambulatory monitoring also offers the possibility of evaluating the duration of efficacy of antihypertensive drug treatment. Some specific advantages of monitoring blood pressure away from the clinic are described below. The disadvantages, which are relatively minor, are also reviewed below.

- Advantages:
  - Reduction of placebo effect
  - Reduction in sample size
  - Avoid unrepresentativeness of clinic pressures
  - Improved selection of patients
  - Evaluation of duration of effect
  - Evaluation of dose - response relationship
  - Evaluation of effects on blood pressure variability
  - Evaluation of effects on diurnal blood pressure profile

- Disadvantages:
  - Inconvenience of multiple recordings
  - Uncontrolled conditions during recordings

7.1 Advantages of Ambulatory Monitoring

7.1.1 Reduction of the Placebo Effect

A placebo has been defined as any therapeutic procedure which is given either deliberately or unknowingly, and which has an effect on a symptom or disease process without any specific activity for the condition being treated. In hypertension research placebos are given for two reasons — to evaluate side effects of treatment and to control for placebo effects on blood pressure. It is the latter which is of concern here.

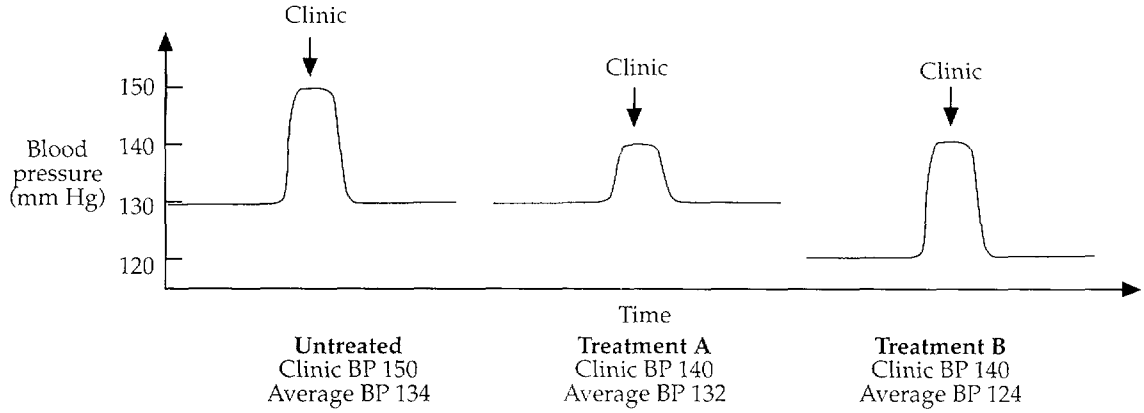
When a placebo is administered chronically there tends to be a gradual and progressive fall of blood pressure, which can be 20 mm Hg or more, but is usually much smaller. In most cases it is not clear to what extent such changes are attributable to the placebo pill, as opposed merely to the tendency for blood pressure to decrease with repeated measurement, which may occur partly from habituation to the measurement procedure and partly from regression to the mean.[231] The size of a placebo effect may also depend on the expectations of the patient — if the patient is told that a particular type of treatment is likely to be most effective, the response is likely to be greater than if they are told that it may have no effect.

When blood pressure is taken by a physician, another relevant factor may be the expectation of the physician. If the physician knows that the patient is taking a placebo, they are less likely to record a fall of pressure than in a truly double-blinded trial.[232]

The placebo response has presented a major problem for the clinical trials of the effects of treating mild hypertension on cardiovascular morbidity. In an Australian trial, almost half the patients originally defined as having mild hypertension on the basis of six clinic measurements spaced over four weeks showed a decrease of pressure to normotensive levels during three years of placebo treatment.[233] Similar findings have been reported for other trials.

An important consideration is whether these changes are confined to the clinic situation or also affect blood pressure at other times. As shown in Figure 7.1, in a hypothetical patient whose blood pressure increases at the time of a clinic visit, a reduction in clinic pressure could occur either because the pressure response to the clinic situation (white coat effect) has diminished, without any change in the pressure at other times, or because there has been a sustained decrease in blood pressure.[234] It seems reasonable to suppose that a placebo response might be of the first type (Treatment A), while a genuinely therapeutic response would require a sustained reduction (Treatment B). These two situations can, of course, be distinguished if blood pressure is measured outside the clinic.

Figure 7.1 — Hypothetical blood pressure response to a clinic visit before and after treatment. In the untreated condition, the clinic visit provokes a pressor response. With Treatment A the clinic pressure is reduced without affecting pressure at other times; Treatment B results in a similar reduction of clinic pressure without affecting the pressor response.



Several studies have compared the effects of placebo therapy on clinic and ambulatory blood pressure (ABP), and almost all have shown that the placebo response observed with the clinic pressures is virtually absent with the ambulatory pressures, or if it does occur, is seen only during the first hour or two of monitoring.[235,236]

These findings clearly indicate that the placebo effect is equivalent to the situation in Figure 7.1b, and has no therapeutic effect other than keeping the doctor (and, perhaps, also the patient) happy. They also suggest that the continued decline of clinic blood pressure observed in the control groups of clinical trials may be an artifact of the clinic situation. In hypertensive patients, clinic pressures tend to decrease with repeated visits even in the absence of a placebo, and this too is not accompanied by any change of ABP.

7.1.2 Reduction in Sample Size

Any investigation of the effectiveness of an antihypertensive therapy must consider the fact that blood pressure is highly variable from one occasion to another. The sample size needed for a crossover or parallel group trial of antihypertensive therapy will depend on three factors, which are predetermined by the investigator. They are: (1) the power of the study (usually 0.8 to 0.9), which is the probability of obtaining a significant result if there is a genuine difference between treatment conditions; (2) the acceptable level of significance (usually $p<0.05$); and (3) the minimum difference between treatments to be detected. Given these requirements, which are independent of the method of measuring blood pressure, the determinant of the required sample size will be the variability of the blood pressure measurement itself, expressed at the standard deviation of the differences (SDD) between measurements. It is clear, then, that the greater the variability of the blood pressure measurement, the harder it will be to detect an effect of treatment, and the larger the sample size required.

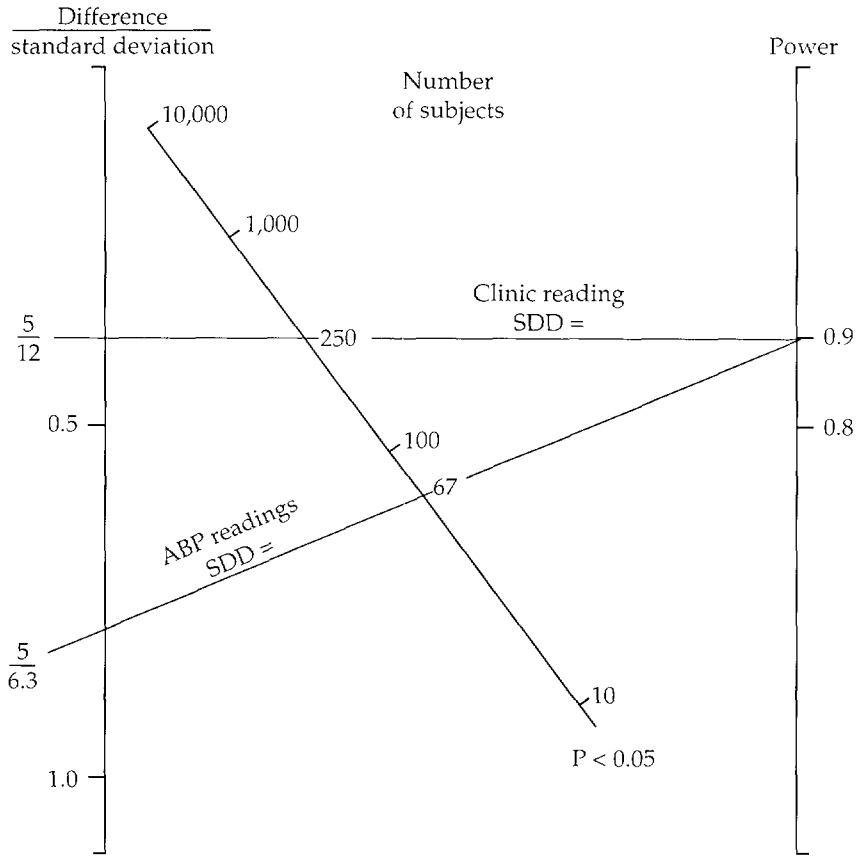
It has been estimated that the SDD for single clinic measurements is about 15 mm Hg for systolic pressure and 10 mm Hg for diastolic or mean pressure.[237] The reliability of a variable measure such as blood pressure can be increased by combining a large number of observations, so that on theoretical grounds alone the use of home or ambulatory monitoring, with which it is easy to obtain multiple readings, should require a smaller sample size. For average daytime ABP the SDD is about 9/6 mm Hg.[238] On this basis a crossover trial designed to detect a treatment effect of 8/5 mm Hg would require 88 subjects if blood pressure was measured by single clinic readings, but only 16 if ambulatory readings were used.

The nomogram in Figure 7.2 shows how the number of subjects needed in a parallel group study designed to detect a treatment effect of a given size would be reduced by using ambulatory rather than clinic readings.[239] This is based on the assumption that the ambulatory recording included at least 20 readings. For a 5 mm Hg treatment effect the number of subjects needed would be 250 using clinic measurements and 67 using ambulatory recordings. For a crossover trial, the number (n) would fall from 61 to 16, according to the equation:

$$N = 10 \times SDD^2 / Difference^2$$

where Difference = 5 mm Hg treatment effect

Figure 7.2 — Nomogram showing the numbers of patients needed in a parallel group study to achieve a 90% chance of detecting a 5 mm Hg treatment effect using either clinic readings (SDD 12.3 mm Hg) or ambulatory readings (SDD 6.3 mm Hg).



A similar set of estimates has been made for elderly patients with isolated systolic hypertension.[240] For a 10 mm Hg treatment effect in a parallel design study, 60 patients would be needed if the effect was assessed by clinic pressures whereas only 54 would be needed using ambulatory pressures. For a crossover study design the corresponding numbers would be 18 and 14.

7.1.3 Avoiding the Unrepresentativeness of Clinic Pressures

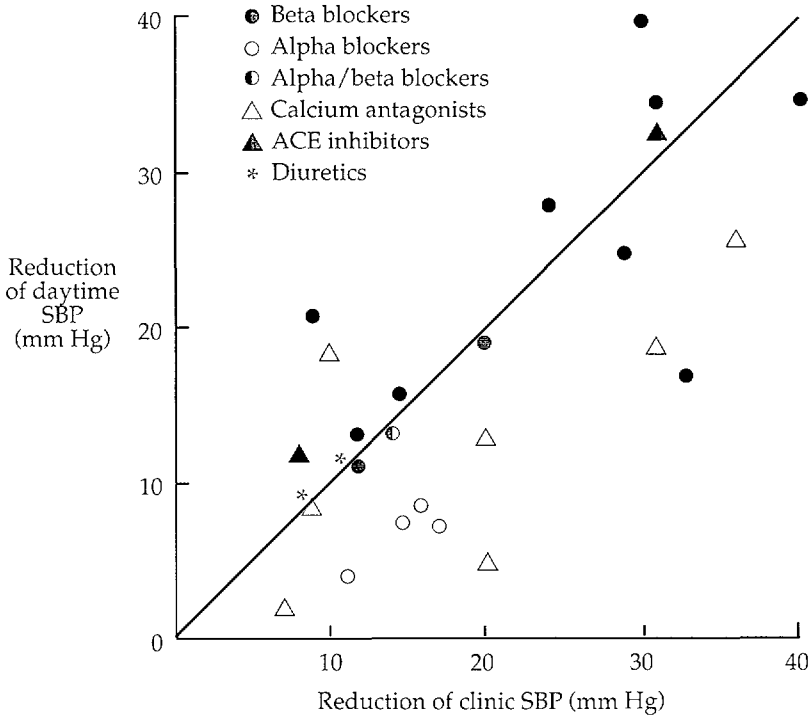
Since the adverse effects of high blood pressure are assumed to depend on the average or integrated level of pressure over long periods of time, the goal of treatment should be to produce a sustained reduction of pressure. Several studies have com-

pared clinic and ambulatory pressures, and while there is a reasonable overall correlation between them (on the order of 0.6 to 0.7), in individual patients there may be a considerable variation between the two.[241,242]

In the majority of studies where the effects of treatment on clinic and ambulatory pressures have been compared, there is reasonably good agreement between the two. Figure 7.3 shows the effects of six different classes of antihypertensive medication (alpha blockers, beta blockers, calcium antagonists, angiotensin converting enzyme inhibitors, and diuretics) on clinic and daytime ambulatory pressures taken from 17 published studies.[243] For most types of medication the overall effects on the two measures of pressure are similar, but there is a tendency for clinic pressures to overestimate the degree of blood pressure control during daily activities in studies using calcium antagonists and alpha blockers.

The discrepancy between clinic and ambulatory pressures has been apparent in several studies of antihypertensive treatment, some of which have shown an effect only on clinic pressures, while others have shown an effect only on ambulatory pressures. Two different medications may have indistinguishable effects on clinic and daytime blood pressure, and yet have quite different effects on nighttime pressure.[244]

Figure 7.3 — Comparison of the effects of six classes of antihypertensive medication on clinic and ambulatory systolic pressure. Each symbol represents the average changes for one type of medication for one study. The diagonal line is the line of identity.



The effects of drug treatment on white coat hypertension have not been investigated very systematically and there are some conflicting observations. Some authors have concluded that white coat hypertension is unaffected by drug treatment, such that both clinic and ambulatory pressures would be lowered to the same extent.[245] Others have found that while the clinic pressure is lowered, there is little effect on ABP.[246,247]

7.1.4 Improved Selection of Patients

The conventional method of selecting patients for inclusion in clinical trials is to use the clinic pressure, which has to be above a certain level. This will tend to favor the inclusion of patients with white coat hypertension, whose response to treatment may be different than the response of true hypertensives. It might be argued that ambulatory monitoring should not only be used to evaluate the effects of treatment, but also to select patients for clinical trials who are hypertensive both in the clinic and during ambulatory monitoring. With a few exceptions, so far this has not been undertaken.

7.1.5 Evaluation of Duration of Effect: Peak and Trough Effects

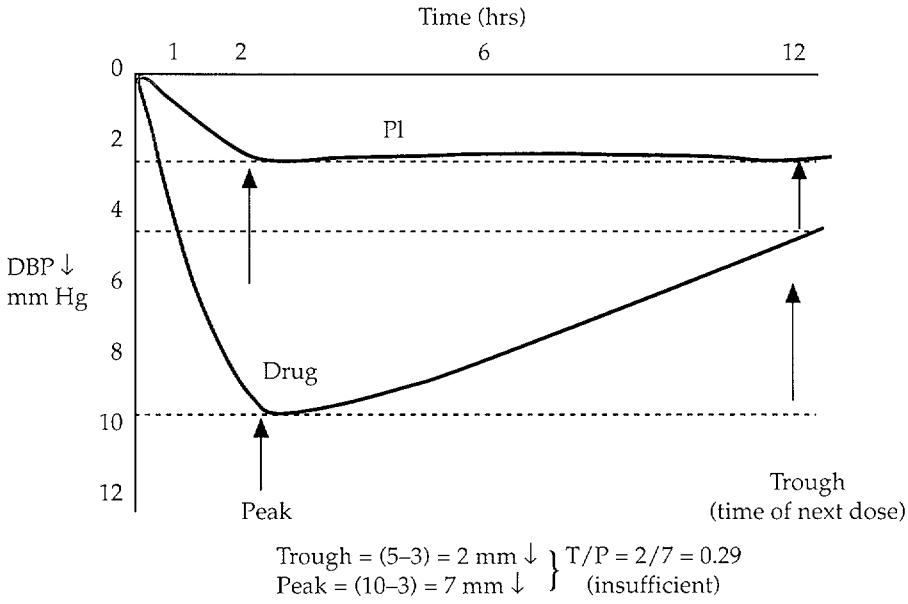
If a medication is taken as a once-daily dose it is important to know whether it is producing a sustained reduction of pressure throughout the day and night. Information about peak and trough effects has become a standard requirement for approval of a new antihypertensive drug by the FDA. The procedure is designed to establish the most appropriate dosing interval. The peak represents the point of maximum blood pressure reduction, and the trough the residual effect just before the next dose is given. In both cases the blood pressure changes with the active drug and placebo are compared, enabling the calculation of the peak-to-trough ratio, as shown in Figure 7.4. The process is normally carried out by making repeated measurements of blood pressure in a standardized clinic setting, which is relatively inconvenient. Thus, the effects of the drug may not be the same in resting subjects as they are during normal daily activities. Ambulatory monitoring is clearly an ideal way to evaluate peak-and-trough effects.

An example of the utility of ambulatory monitoring in this respect is provided by a study showing that quinapril, an angiotensin converting enzyme inhibitor with a short plasma half-life (three hours), can nevertheless lower blood pressure for a full 24 hours when given in a single daily dose.[248]

7.1.6 Evaluation of Dose-Response Relationships

The establishment of the minimum effective dosage of any antihypertensive agent is clearly an important objective, both from the point of view of reducing the costs and side effects of treatment. The conventional method of assessing the dose-response relationship of antihypertensive medications, which is done by progressively increasing

Figure 7.4 — Hypothetical blood pressure changes following active drug and placebo, from which peak-to-trough ratio can be estimated.



the dose until a desired reduction of clinic pressure is reached, tends to lead to an overestimation of the effective dose. This would occur because of the unreliability (high SDD) of clinic pressures. Even if the medication had no effect on blood pressure, the high variability of the clinic pressures would lead to a significant number of patients being classified as responders on the second visit, and a similar proportion would be classified as nonresponders because their clinic pressures would be higher. If the nonresponders are given a bigger dose, a similar proportion of them will be classified as nonresponders on the next visit, leading to a further escalation of the dose. A more reliable estimate of the dose-response relationships of a medication could be obtained by using ambulatory monitoring, and by exposing all patients to all doses.

7.1.7 Evaluation of the Effects of Morning vs. Evening Dosing

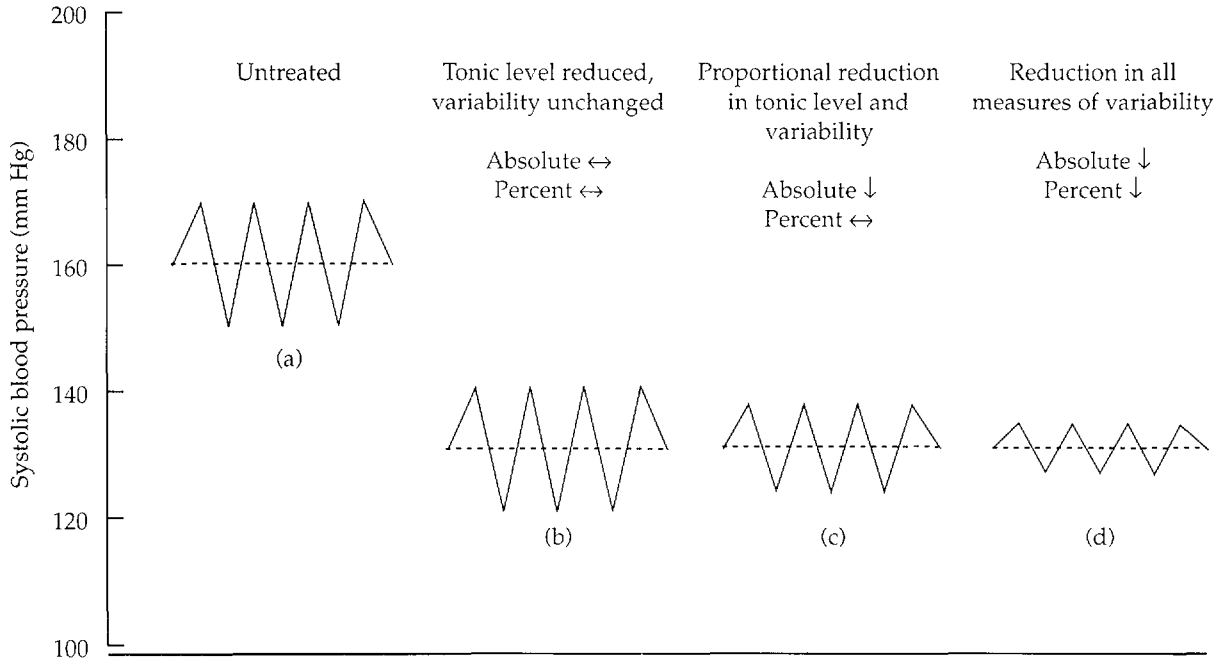
Many antihypertensive medications are given as single daily doses, usually in the morning. However, theoretical concerns about the possible adverse effects of the rise of blood pressure that accompanies getting up in the morning suggest that evening dosing might be preferable, and there are some studies with ambulatory monitoring that show that this may indeed be the case.[248] Morning dosing of enalapril lowers blood pressure relatively more during the day than during the night, whereas the reverse is true of evening dosing.[249]

7.1.8 Evaluation of the Effects of Treatment on Blood Pressure Variability

Blood pressure can be regarded as a steady-state or true pressure about which phasic variations occur. This variability can be measured both in absolute terms, (e.g., by the standard deviation) or in relative (percentage) terms (e.g., by the coefficient of variation). As shown in Figure 7.5, antihypertensive treatment could affect the tonic and phasic components of blood pressure in three ways: (1) the tonic level may be lowered without any reduction in variability (Figure 7.5b); (2) there could be a proportional reduction in the tonic level and the variability in which case the absolute, but not the relative measures of variability would be reduced (Figure 7.5c); and (3) the tonic level and all measures of variability might be lowered (Figure 7.5d). This last effect would be regarded as a true reduction of blood pressure variability as a result of treatment.

One of the undoubted functions of the sympathetic nervous system is to produce short-term increases of blood pressure such as occur during physical and mental arousal. It might be thought, therefore, that antihypertensive drugs which interfere with the functioning of the sympathetic nerve system (e.g., alpha or beta blockers) would reduce blood pressure variability over 24 hours (Figure 7.5d), whereas those that act independently of it (e.g., diuretics or converting enzyme inhibitors) would not. One of the surprising findings of ambulatory monitoring studies has been that most antihypertensive agents have little or no effect on short-term blood pressure variability, regardless of their mode of action.[250-253]

Figure 7.5 — Hypothetical effects of antihypertensive medication on blood pressure. In untreated state (a), blood pressure is depicted as oscillations around a steady state level; (b), (c), and (d) show different treatment effects which produce some reduction of average pressure, but different effects on variability.



7.1.9 Effects of Treatment on the Diurnal Blood Pressure Profile

It is clear that the majority of antihypertensive agents have relatively little effect on the diurnal rhythm of blood pressure, although there is a tendency to lower pressure a little more during the day.[254] Typical examples are shown in Figure 7.6.

The two agents that do appear to have a preferential effect on the increase of blood pressure during the day are labetalol and methyldopa.[255,256] The former blocks both alpha and beta adrenergic receptors, while the latter inhibits central sympathetic outflow. The increased pressure during the day is almost certainly largely mediated by the sympathetic nervous system, and the fact that both limbs (alpha and beta) have to be blocked to impair this increase may be an example of the principle that the central nervous system will increase pressure by whatever mechanism is available.[257] The effects of labetalol are shown in Figure 7.7.

Figure 7.6 — The effects of lisinopril once daily on the diurnal profile of diastolic pressure: before (●) and after (■).

Used with permission from Whelton A, Miller WE, Dunne, Jr. B, et al. Once-daily lisinopril compared with twice-daily captopril in the treatment of mild to moderate hypertension: Assessment of office and ambulatory blood pressures. *J Clin Pharmacol.* 1990;30:1074-1080.

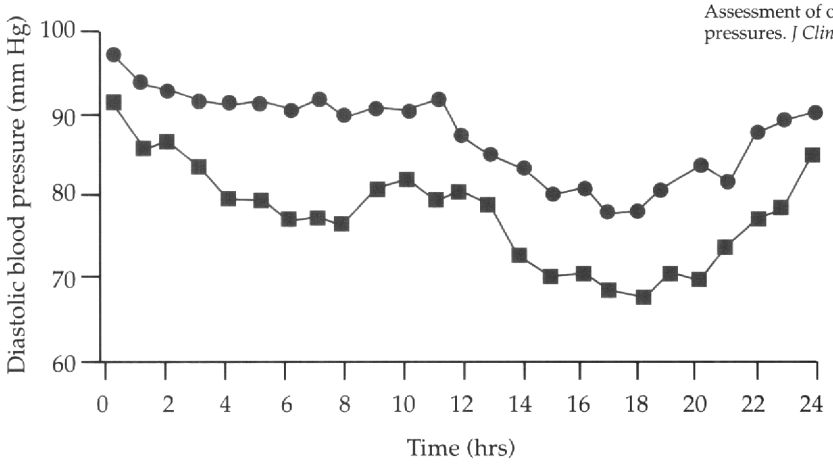
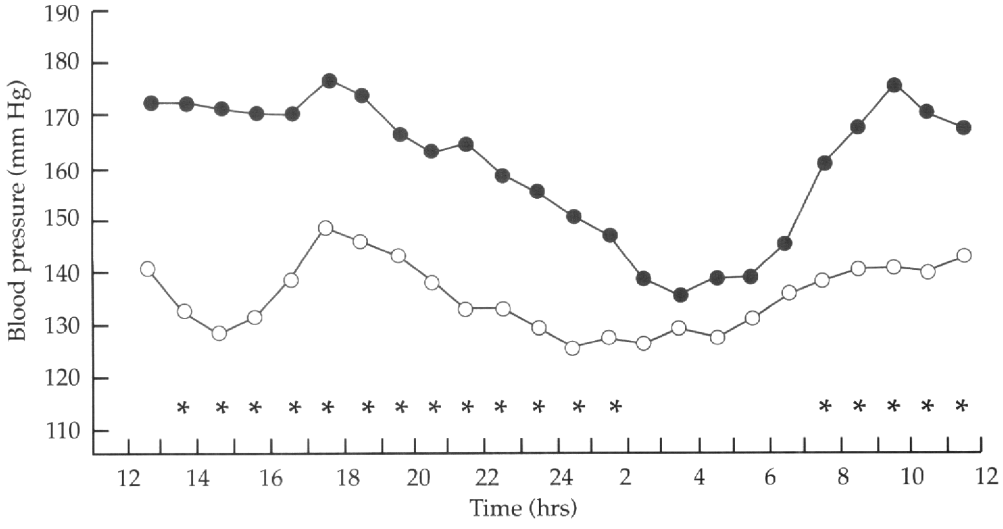


Figure 7.7 — The effects of labetalol on ambulatory pressure: placebo (●) and labetalol (○). A significant reduction in blood pressure is noted by an asterisk along the base of the graph.



7.1.10 Evaluation of the Effects of Nonpharmacologic Treatment

With the acknowledgement of the expense and side effects associated with pharmacologic treatment of hypertension, there has been considerable interest in the use of nonpharmacologic methods. These have taken a variety of forms, but may be loosely classified in three major groups — dietary, exercise, and relaxation. A common feature of all is that they require an active and sustained behavioral change made by the patient. A potential concern with all of them is the possibility of placebo effects.

Ambulatory monitoring has been used infrequently to evaluate the effectiveness of nonpharmacologic treatments, but some interesting findings are beginning to emerge. Exercise, for example, may lower blood pressure during the day, but not during the night.[258]

7.2 *How Should the Effects of Treatment be Analyzed?*

The previous discussion makes it clear that ambulatory monitoring enables much more detailed information to be acquired about the effects of an antihypertensive agent than clinic measurements, but there is as yet no standard method for analyzing or expressing the results. A number of methods have been used. In general, the information that is required can be listed as follows: (1) effect on the overall or average level of blood pressure; (2) peak and trough effects; (3) effects on diurnal profile (long-term variability); and (4) effects on short-term variability. These are reviewed below.

- Effects on Average Pressure: Average 24-Hour Blood Pressure/Average Daytime Blood Pressure
  - Percent readings above 140/90 mm Hg (diastolic pressure load)
  - Running averages
- Peak-and-Trough Effects: Consecutive Hourly Averages
  - Fourier analysis
- Effect on Diurnal Profile: Awake-Sleep Blood Pressure Cosinor Analysis
  - Area under curve
- Effects on Short-Term Variability: Standard Deviation, etc.
  - Histogram
  - Response to standard challenges

7.2.1 Effects on Average Pressure

The most widely used method has been to express the effects of the drug on the average 24-hour or daytime ABP.[259,260] This has the advantages of being both simple and relevant.

Another method has been to describe the effects on the percentage of readings above an arbitrary value, e.g., 140/90 mm Hg for daytime values and 120/80 mm Hg for nighttime.[261]

7.2.2 Peak and Trough Effects

In principle, the analysis of peak and trough should be quite simple, using serial measurements of blood pressure before and after each dose of the drug. With ABP recordings several clinicians have analyzed consecutive hourly averages (e.g., by multiple *t* tests) for looking at the duration of effect.[262,263] This approach has several problems. First, the use of multiple *t* tests is inappropriate for data which are not independent of each other. Second, with noninvasive recorders it is common to obtain between two and four readings per hour, so that the reliability of an hourly average may be quite low.

The fact that there is a consistent diurnal variation of blood pressure adds a significant complication to this analysis. It may be more difficult to detect a subtle effect on blood pressure during the working day when blood pressure is relatively labile than during the evening when it is more stable.

7.2.3 Area Under the Curve

Area under the curve (AUC) is a traditional method of quantifying the effects of a drug on blood pressure which compares the area of the plot of blood pressure against time with and without the drug. It gives much the same information as the average pressure, and is an insufficient description on its own, because two drugs with similar AUCs may have quite different time courses of action.[264]

7.2.4 Effects on Diurnal Profile

Many studies have concluded that antihypertensive medications have little effect on the diurnal profile, but in general have not performed any formal analysis to justify this statement. One simple way of evaluating it would be to compare the difference between the average waking and sleeping pressure before and after treatment.

Cosinor analysis has also been used for this purpose. This technique is described in Section 11.0 and, while mathematically appealing, presupposes that the diurnal rhythm is basically a sine (or cosine) wave, which it clearly is not.

7.2.5 Effects on Hourly Averages

A popular technique has been to examine the effects on consecutive hourly average blood pressure values, which is another way of looking at changes in the diurnal profile. However, it has been shown that the reproducibility of individual hourly average values is not very good, partly because activities at a particular time of day are unlikely to be identical on different occasions, and also because there are usually no more than four readings on which to base each hourly average value.[265]

7.2.6 Running Average Analysis

A convenient method for reducing the variability and extracting an overall trend from a time series of measurements is to compute running averages. This technique has been used for analyzing treatment effects, including estimates of the average reductions, and peak and trough effects.[266]

7.2.7 Effects on Short-Term Variability

The most widely used measures of blood pressure variability have been the standard deviation and coefficient of variation. As discussed in Section 3.0, short-term variability cannot be reliably evaluated with noninvasive recorders. It is, however, possible to examine the effects of specific activities on blood pressure, and to see how these changes are affected by treatment.

7.3 Disadvantages of Ambulatory Monitoring

The main limitation of ambulatory monitoring for the evaluation of treatment is the number of recordings that can be performed on any one patient. Two or three per hour is usually the limit, and patient compliance falls off sharply if more are attempted. Thus, it may not be easy to determine how quickly a drug takes effect, and self-monitoring may be preferable.

The second potential problem is the variability of blood pressure on different recording days. The more ambulatory the patients, the more variability (and also artifact) is likely to occur, which may confound the analysis of the effects of the drug. An extreme example of this would occur if one recording was made on a work day, and another on a nonwork day. Thus, the activities of the patients should be standardized as much as possible from one recording to another. These disadvantages are relatively minor compared to the advantages.

8.0 IMPLEMENTING AN AMBULATORY BLOOD PRESSURE MONITORING PRACTICE

Although ambulatory monitoring is rapidly gaining favor with clinicians, it has not yet been recognized as a clinically valid tool by many professional organizations, and its costs are not reimbursed by many third-party payers. The rationale for its acceptance rests on two issues — the recognition that it can provide unique and clinically important information that cannot be provided by other procedures, and that it can provide information more cost-effectively than other methods. As discussed in Section 4.1, ambulatory monitoring certainly can provide unique information, but its clinical importance remains unresolved.

A recent survey of practice habits of 65 community and hospital-based physicians in Connecticut concluded that the physicians were using the procedure for appropriate indications, and that data obtained from the monitoring significantly improved the management of the patients.[267] The main indications for ordering the tests were the evaluation of borderline hypertension (27%), the assessment of drug treatment (25%), white coat hypertension (22%), and resistant hypertension (16%).

8.1 Cost-Effectiveness

The issue that has received the most attention for establishing the cost-effectiveness of ambulatory monitoring has been its use in detecting patients with white coat hypertension, in whom the costs of performing the monitoring would be offset by savings in the costs of antihypertensive medication. On this basis it has been estimated that the procedure is potentially cost-effective, although its unrestricted use could clearly be extremely costly and wasteful.[268,269] Yarows et al. performed an analysis of patients attending a general practice in Michigan who were evaluated with ABP monitoring, and concluded that the costs of the monitoring would exactly offset the savings in medication costs that would result from the patients found to have white coat hypertension, who would otherwise have been treated.[270] They assumed that the ABP monitoring would cost $188 per monitoring; the average cost of antihypertensive medications for one year was $578.

8.2 Recognition by Professional Organizations

Several professional organizations have reviewed the field of ambulatory monitoring and issued statements concerning its clinical utility.

8.2.1 National High Blood Pressure Education Program

This report, published in 1990, concluded that ABP monitoring presents an opportunity to obtain information about blood pressure load over time and during circumstances that are not otherwise measurable.[271] It stated that while ABP monitoring is not necessary for the diagnosis of the majority of hypertensive patients, it can provide important clinical information in specific problems, including white coat hypertension and episodic hypertension or hypotension.

8.2.2 American College of Physicians

This organization issued a position paper in 1993 that concluded that "the available evidence does not warrant widespread dissemination or routine use of automated ABP measurement at this time. On the other hand, we support a more circumspect use of such devices for research and for the care of subgroups of hypertensive patients with specific clinical problems."[272]

8.2.3 Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure

Published in 1993, this report included a list of clinical indications for ambulatory monitoring, and stated that while ambulatory monitoring is a unique tool for research and for extended assessment of particular hypertensive patients with special clinical

problems, it is not necessary for the routine diagnosis and management of most patients.[273]

8.2.4 American College of Cardiology

The Hypertensive Diseases Committee of the American College of Cardiology issued a brief report in May 1994 which stated that ambulatory monitoring is a mature, clinically useful technology for the management of selected hypertensive patients, and that if used with appropriate restraint can be cost-effective.[274]

8.3 *Selecting Patients for Ambulatory Monitoring*

The clinical indications for ambulatory monitoring are reviewed in Section 4.0. Ambulatory blood pressure measurement is not normally appropriate as an initial evaluation, but only after the routine tests have been performed and the patient's blood pressure has been measured over several clinic visits. The most common general category of patients in whom ambulatory monitoring is clinically helpful are those where there is a suspicion that the clinic readings may be unrepresentative of true blood pressure.

There is a minority of patients in whom the procedure is contraindicated, either for technical reasons (e.g., major arrhythmias or excessive obesity) or because of severe anxiety.

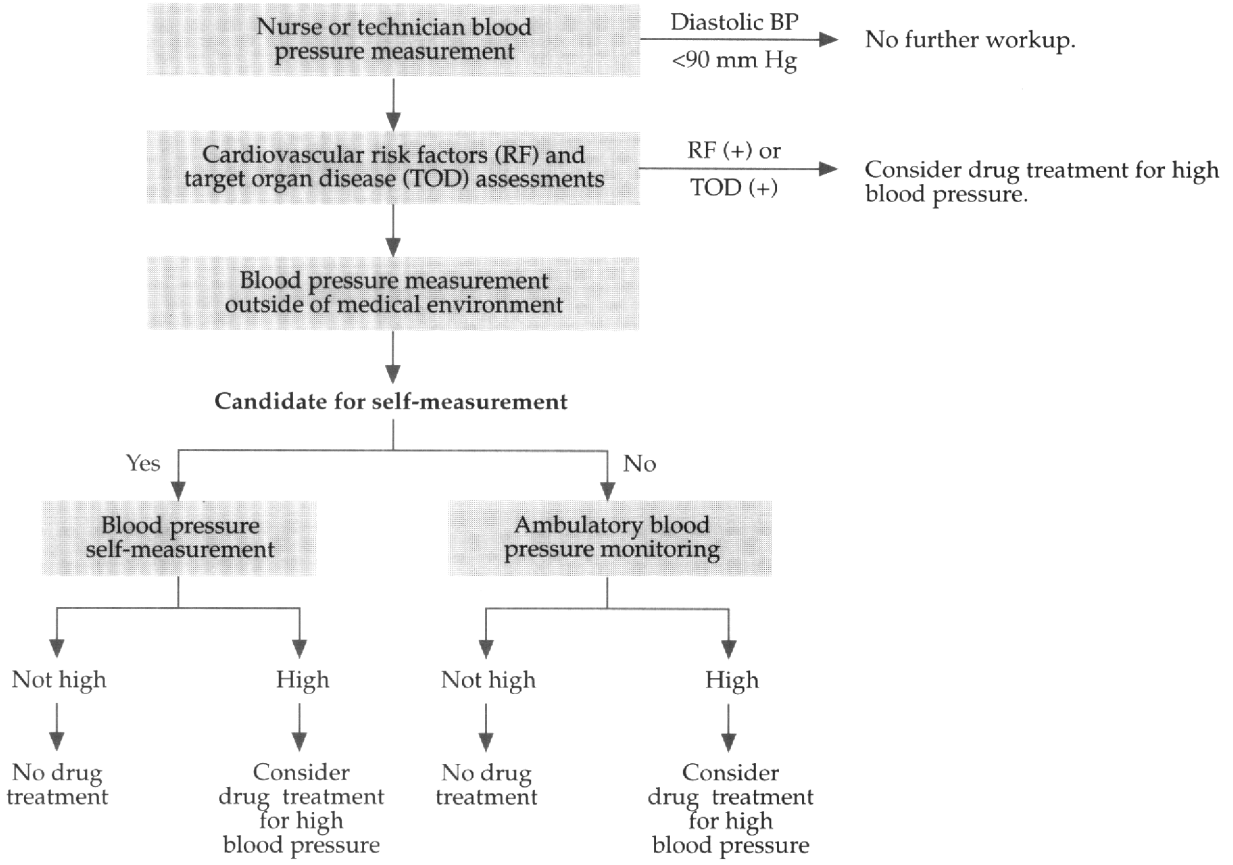
An appropriate strategy for using ambulatory monitoring is outlined in Figure 8.1 and involves the following steps:

- If the clinic diastolic blood pressure measured by the physician is in the range of 90 mm Hg to 104 mm Hg, repeat measurements are indicated at one or more subsequent visits, which might be taken by a technician or nurse to minimize the white coat effect and provide readings by a technique similar to that used in most clinical hypertension trials.

- If the blood pressure is still elevated above 140/90 mm Hg on repeat measurement, patients can be stratified on the basis of target organ damage (e.g., left ventricular hypertrophy or albuminuria) and associated risk factors (e.g., diabetes or hyperlipidemia). Those with evidence of these may be prescribed pharmacological or nonpharmacological treatment.

- Patients whose clinic blood pressures remain elevated but have no target organ damage or other risk factors are candidates for self-measurement or ambulatory monitoring (Figure 8.1). While the former is less expensive, it requires some training of the patient, and there is less prognostic information relating to it than with ambulatory monitoring.

Figure 8.1 — A proposed strategy for utilizing ambulatory monitoring.



8.4 Interpretation of the 24-hour Profile

Analysis of 24-hour recordings for routine clinical purposes is relatively straightforward, although there is still no consensus as to what are the limits of a normal ABP. The following steps are recommended:

- Check whether the recording is technically adequate. There should be at least four hours of daytime readings and at least two hours during the night. Usually there is much more than this. The number of errors should be below 10%.

- Examine the graphic display of the blood pressure readings. There is usually a pronounced diurnal rhythm of pressure with a decrease of about 10% during the night. If the profile is flat, the patient may be a nondipper (see Table 4.2 and Figure 4.4). There are commonly some isolated high readings. These may be associated with physical activity, but may also be artifacts.

- Examine the average values of 24-hour, daytime and nighttime pressure. An alternative method of evaluating the overall level of ABP is the blood pressure load (the percent of readings over 140 mm Hg for systolic and 90 mm Hg for diastolic pressure). This is also displayed on the printout. Suggested normal ranges are shown in Table 8.1.

Since the daytime and nighttime pressures are estimated on a fixed time basis, they do not necessarily correspond to the waking and sleeping average values.

Table 8.1 – Upper Limits of Normalcy of Average Ambulatory Blood Pressure and Load

BP Measure	Probably Normal	Borderline	Probably Abnormal
Systolic average (mm Hg)			
24-hour	<130	130-134	>135
Day	<135	136-139	>140
Night	<120	121-124	>125
Systolic load			
Day	<20%	21-39%	>40%
Night	<20%	21-39%	>40%
Diastolic average (mm Hg)			
24-hour	<80	81-84	>85
Day	<85	86-89	>90
Night	<75	76-79	>80
Diastolic load			
Day	<20%	21-39%	>40%
Night	<20%	21-39%	>40%

Threshold levels for estimate of load are 140/90 mm Hg during the day and 120/80 mm Hg at night.

8.5 Costs

The published resource costs of performing a single test (including costs for equipment and personnel) have been estimated to be between $100 and $150.[268] Charges for ABP monitoring can vary from $100 to $300 or more. The estimate of the resource costs for a clinical ambulatory monitoring service can be based on the assumptions shown in Table 8.2.

Table 8.2 – Resource Cost Model for Clinical ABP Testing

1. General assumptions

a. 200 procedures performed per year
b. 2 ABP monitors, each costing $3,500
c. Analysis station/printer costing $2,000
d. Cost of supplies (batteries, paper, ribbon, etc.) $600
e. One hour technician time per procedure billed at $14.40 per hour with fringes, or at an annual rate of $30,000
f. Physician's interpretation fee at $30

2. Technician time allocations

Initial patient visit	20 minutes
- Equipment demonstration and procedure instructions	
- Patient hook-up	
- Complete 3 correlation readings	
Return patient visit	15 minutes
- Complete 3 correlation readings	
- Remove monitor	
Follow-up activities	15 minutes
- Download data into computer	
- Generate report	
- Recordkeeping	
- Equipment maintenance and storage	
Actual time	50 minutes
20% efficiency variable	10 minutes
Technician time allocated per procedure	60 minutes

3. Annualized ABP procedure costs

Two monitors depreciated over 3 years	$2,333.00
Analysis station/printer depreciated over 3 years	667.00
Annual maintenance fee allocation	467.00
Supplies	600.00
Billable technician time: 200 hours at $14.40/hr	2,880.00
Total annualized technical cost	6,947.00
Technical cost per procedure	34.74
Physician's interpretation fee per procedure	30.00
Total cost per ABP procedure	64.74

Figure 8.2 — An example of a medical necessity letter describing ambulatory monitoring to third-party payers.

We are now providing, as a service to our customers, ambulatory blood pressure monitoring. This procedure provides a fully automated measurement of blood pressures taken at frequent intervals during a 24-hour period. It is similar in concept to the Holter monitor. A battery-operated lightweight device is attached to the patient and is programmed to measure and record blood pressures as frequently as every 10 minutes or as infrequently as every hour. The data is then retrieved in numerical or graphical format. The patient keeps a diary similar to that used in Holter monitoring, so that symptoms occurring while pursuing normal activities may be correlated with blood pressure readings. The device can be triggered by the patient at any time to check the blood pressure while symptoms occur.

The advantages of ambulatory blood pressure monitoring have been well documented in medical literature. It is generally recognized that spot checks of blood pressure in a physician's office may not represent blood pressure readings taken in the home or work environment. This discrepancy may lead to important errors in diagnosis and management. Clinical trials have demonstrated that ambulatory blood pressure measurements can distinguish cardiovascular risks in patients who are otherwise indistinguishable by office blood pressure measurements and by other known risk factors for cardiovascular morbidity and mortality such as age, sex, and pre-existing disease states.

Ambulatory blood pressure monitoring is of particular use in certain subsets of patients. Patients with borderline or labile hypertension may, at times, be over treated. Indeed, the risks of treatment in those with mild hypertension have received emphasis in recent medical literature. Ambulatory blood pressure monitoring provides a sensible approach to distinguish those who truly need therapy from those who do not, and can spare those who do not from unnecessary risks.

A second category of patient who may have particular benefit from ambulatory blood pressure monitoring includes those who are symptomatic when treated with a variety of antihypertensive agents. Some of these patients may have hypertension only in the physician's office. Episodes of hypotension while on therapy may be avoided by blood pressure measurements recorded outside the medical setting.

While it is unusual to find that ambulatory blood pressures are higher than those recorded in a physician's office, for some patients work-related stress or other factors may actually result in higher blood pressures in the ambulatory setting during certain periods of the day. Ambulatory blood pressure monitoring enables the physician to obtain a realistic profile of the patient's blood pressure during a typical 24-hour period and to tailor therapy accordingly.

Ambulatory blood pressure monitoring is not only useful, it is also cost-effective. Patients are spared not only the side effects of over treatment, but also its cost. Perhaps this is why many insurance carriers now provide reimbursement for ambulatory blood pressure monitoring.

Our service for ambulatory blood pressure monitoring includes 24-hour recording of data with a fully automated device, analysis in graphical and numerical form, interpretation, and report.

Very truly yours,

Figure 8.3 — An example of a medical necessity letter justifying the use of ambulatory monitoring of a particular patient.

Patient:_____

Contract No., Policy No., or HIC No._____

Dear Benefits Manager:

I have been treating (patient name) since (date) for his/her (diagnosis). Treatment has included (brief clinical summary). In my opinion, the status of the patient's condition warrants the use of an ambulatory blood pressure monitor to:

1. Determine episodic, borderline, or uncontrolled hypertension, as well as syncope or orthostatic hypertension;

2. Help assess severity of hypertension in relation to end organ damage;

3. Determine the efficacy of prescribed medication, dosage, and frequency of dose;

4. Assess the effects of multiple drug interaction; and

5. Determine the presence or absence of hypertension (patient has demonstrated office hypertension only).

SpaceLabs Medical's automated ambulatory blood pressure monitoring system has been prescribed to record my patient's blood pressure measurements for a 1-, 2-, or 3-day period. As a result of this test, I have determined the best course of treatment is (summary).

Sincerely,

8.6 Reimbursements

In the U.S., third-party reimbursement (when provided) may vary from $80 to $450. Many private insurance companies do not reimburse the cost of ambulatory monitoring, but the situation is very variable. Reimbursement by Blue Cross/Blue Shield differs from state to state. Medicare provides no reimbursement. This situation is showing little change with time. Figures 8.2 and 8.3 are examples of medical necessity letters that can be sent to third-party payers. For other countries outside the U.S., various reimbursements do exist.

8.7 Ambulatory Monitoring Billing Information

The following information should help in maximizing possible third-party reimbursement for ambulatory monitoring.

The U.S. Physician's Current Procedural Terminology, 4th Edition (CPT-4) guide gives the following codes for ambulatory monitoring:

- 93784. Ambulatory blood pressure monitoring utilizing a system such as magnetic tape and/or computer disk, for 24 hours including recording, scanning analysis, interpretation, and report
- 93786. Recording only
- 93788. Scanning analysis with report
- 93790. Physician review with interpretation and reports.

The International Classification of Disease, Volume 9 (ICD-9) lists diagnostic codes related to hypertension as:

- 401. Essential hypertension
- 402. Hypertensive heart disease
- 403. Hypertensive renal disease
- 404. Hypertensive heart and renal disease
- 405. Secondary hypertension.

8.8 *Training*

The recordings are typically carried out by a technician specially trained for the purpose. The level of expertise required is no greater than for performing other medical procedures, such as ECGs. The reference manuals provide all the necessary information. It is also important that the technician is trained in accurate blood pressure measurement, for which videotapes are commercially available. Technician performance should then be tested against a trained observer, which can conveniently be done using a double-headed stethoscope.

9.0 A REVIEW OF STANDARDS FOR AMBULATORY BLOOD PRESSURE MEASUREMENT

The subject of blood pressure measurement has had a checkered history. When the technique was first introduced at the turn of the century it attracted considerable attention and was considered to be of such importance as to merit the publication of a 300-page book by Theodore Janeway in 1904. Indeed, the subject has stimulated a number of people in hypertension research to write major works on the subject over the intervening years, the last decade having been particularly notable in this regard because of the development of ambulatory measurement. There are two aspects of blood pressure measurement that require consensus — that the way in which the technique is performed is standardized and that the devices used for measuring blood pressure are accurate.

9.1 Recommendations on the Technique of Blood Pressure Measurement

Though there were many books written on the technique of blood pressure measurement in the early years of the century, the first official recommendations came jointly from the American Heart Association (AHA) and the Cardiac Society of Great Britain and Ireland in 1939. These recommendations have been revised regularly by the AHA. The U.S. National High Blood Pressure Education Program was founded in 1972 and has published recommendations on blood pressure measurement, including an important report on ambulatory blood pressure (ABP) measurement.

In 1959, the World Health Organization (WHO) issued recommendations which were revised in 1962. The WHO and the International Society of Hypertension jointly produced recommendations for the management of mild hypertension in 1988, with recommendations for the measurement of blood pressure.

The World Hypertension League (WHL) was founded in 1984 with the objective of bringing together and stimulating the formation of societies committed to the control of hypertension throughout the world. Beginning with only seven national organizations, it now comprises 48 member organizations in the developed and developing world. It reaches over 12,000 doctors with its newsletter and *In Focus* statements making recommendations on various aspects of blood pressure management, including the technique of blood pressure measurement. The WHL publishes, annually, a useful yearbook summarizing its activities and the activities of its member organizations. The WHL cooperates closely with WHO, the International Society of Hypertension, the scientific organization which unites hypertension scientists from all parts of the world, and the European Society of Hypertension, which performs a similar function in Europe.

Many countries publish recommendations on the technique of blood pressure measurement. A list of the names and addresses of national organizations and a summary of their activities can be found in the WHL Yearbook 1993. An example of a national organization active in publishing recommendations is the British Hypertension Society (BHS), which published recommendations for measuring blood pressure in adults and children in 1986 and then revised in 1990. These recommendations are available in booklets. The BHS has also produced a video that demonstrates the technique of blood pressure measurement and provides an assessment of observer accuracy.

9.2 Controversial Aspects of Blood Pressure Measurement

From a review of international recommendations, it is possible to identify the areas of greatest concern in the technique of blood pressure measurement, and they are discussed below.

9.2.1 Observer Training

The measurement of blood pressure in clinical practice is dependent on the accurate transmission and interpretation of a signal (Korotkoff sound or pulse wave) from a subject via a device (the sphygmomanometer) to an observer. The successful outcome

of this complex interaction requires that the observer is competent in performing the technique of blood pressure measurement. The procedure is fraught with sources of potential error which may arise in the observer, the subject, the sphygmomanometer, or in the overall application of the technique. Training observers is a cause for considerable concern because the technique of blood pressure measurement is all too often poorly taught in medical and nursing schools.

9.2.2 Bladder Dimensions

Of the many controversial issues in hypertension few can rival that of determining the optimum dimensions of the inflatable bladder for a particular arm circumference. It is fair to say that a review of the considerable literature on the subject often serves to confuse rather than clarify. What is clear is that the use of cuffs containing inappropriate bladders for the arms in which blood pressure is to be measured is a serious source of error that inevitably leads to incorrect diagnosis in practice and erroneous conclusions in hypertension research. There is unequivocal evidence that either too narrow or too short a bladder will cause overestimation of blood pressure and there is equivocal evidence that too wide a bladder causes underestimation of blood pressure. The former has the effect in clinical practice of over-diagnosing hypertension, and the latter of under-diagnosing the disease. Either eventuality has serious implications for the epidemiology of hypertension and clinical practice.

The consensus from the literature is that a cuff should contain an inflatable bladder that encircles the arm. A cuff containing a 12 x 25 cm bladder will give accurate blood pressure measurements in the majority of adults. For subjects with large arms, the 1994 AHA recommendations are 13 x 30 cm bladders for arms measuring in the range of 27 to 34 cm and 16 x 38 cm bladders for arms measuring 35 to 44 cm.

9.2.3 Diastolic Dilemma

Recommendations of blood pressure measurement have vacillated for many years on the issue of the diastolic end-point — the so-called diastolic dilemma. Phase IV (muffling) may coincide with, or be as much as 10 mm Hg higher than, Phase V (disappearance), but usually the difference is less than 5 mm Hg. Phase V correlates best with intra-arterial pressure, but general acceptance of the silent end-point has been resisted until recently because in some groups of patients (e.g., children and pregnant women, anemic or elderly patients) the silent end-point may be significantly below the muffling of sounds. The arguments for and against selecting one phase over the other have been well summarized and there is now a general consensus that disappearance of sounds (Phase V) should be taken as diastolic pressure except when sounds persist to 0 or to very low levels.

9.2.4 Millimeter of Mercury or SI Units?

Apart from the Australian Standards Organization which recommends that the kilopascal should be displayed alongside the millimeter of mercury, there seems to be general international agreement that the millimeter of mercury should be retained as the unit of measurement for blood pressure.

9.2.5 Which Technique is Best — Clinic, Home or Ambulatory?

Because of white coat hypertension it has become recognized that the conventional technique of office or clinic measurement of blood pressure may give an erroneous impression of an individual's true blood pressure, no matter how accurate the conventional technique may be. Measurement of blood pressure in the home or workplace by either the subject, a relative, or friend can provide useful information on blood pressure behavior and also identify those subjects with white coat hypertension. This technique has limitations in that the devices available are often inaccurate, the measurements are necessarily limited in number and may be influenced by observer bias, and the nocturnal blood pressure profile cannot be obtained. Twenty-four-hour noninvasive ABP monitoring, on the other hand, has the advantage of being accurate, free of observer bias, and capable of providing frequent measurements as well as giving a profile of nocturnal blood pressure. However, self-measurement of blood pressure is inexpensive, whereas 24-hour ABP monitoring remains, for the time being, expensive and out of reach of many poorer countries. A reasonable consensus from the literature would be that where only conventional measurement is available, measurement should be repeated frequently over many months before diagnostic or therapeutic decisions are made; where 24-hour noninvasive ABP monitoring is available, it should be used in patients in whom the diagnosis is unclear — those suspected of having white coat hypertension, those with borderline hypertension, those whose hypertension appears to be resistant to treatment — and as a guide to drug therapy in patients receiving antihypertensive medication. Where 24-hour ABP monitoring is not available, self-measurement of blood pressure should be used in the situations listed for ABP monitoring to obtain a profile of blood pressure behavior outside the clinical environment.

In 1990, the National High Blood Pressure Education Program Coordinating Committee drew up guidelines on ambulatory monitoring. The proceedings of the Second International Consensus Meeting on 24-Hour Ambulatory Monitoring in Dublin in 1992, which contain recommendations on many aspects of ABP monitoring, have been published, as have the proceedings of the third meeting held in New Orleans in 1992.

9.3 Recommendations on the Accuracy of Blood Pressure Measuring Systems

In recent years there has been considerable concern about the inaccuracy of blood pressure measurement in general, partly because so many current devices, such as ambulatory systems, are very expensive — ranging from $4,000 to in excess of $20,000 for one recorder and decoding system, depending on accessories, computer facilities, and software options purchased. The charge for 24-hour ambulatory recordings also reflects the high cost of ambulatory equipment. There are also substantial costs in operating an ABP service. However, the potential savings associated with ambulatory monitoring must be offset against these costs. It is estimated that the U.S. market for cardiovascular drugs, which is growing by 9% annually, has risen from $4 billion in 1986 to nearly $6 billion in 1991. The largest therapeutic category is hypertension, and it has been estimated that antihypertensive drug sales in the U.S. have risen from $2.5

billion in 1987 to over $3 billion in 1991. Ambulatory blood pressure monitoring may reduce these costs substantially by reducing drug prescribing. The complex issue of cost/benefit analysis is presently undergoing study.

If high standards of performance and accuracy are not demanded, continued uncontrolled marketing of expensive blood pressure measuring systems will inevitably result in the manufacture and sale of inaccurate devices. This has clear implications for clinical practice, the most important of which is inappropriate diagnostic and management decisions. For many years centers interested in the measurement of blood pressure tested new devices according to a variety of validation protocols. The value of these studies was greatly diminished by a lack of standardization that did not permit comparison of one device with another. In an attempt to standardize validation, two protocols have been published for the evaluation of blood pressure measuring devices — the Association for the Advancement of Medical Instrumentation (AAMI) standard, first published in 1987 and recently revised, which is accepted by the Food and Drug Administration as the national standard in the U.S., and the protocol of the BHS, first published in 1990 and also recently revised. These protocols have certain similarities but there are also differences and it is useful to contrast their features.

9.4 Comparison of British Hypertension Society and Association for the Advancement of Medical Instrumentation Protocols

The revised AAMI protocol for validation of electronic or automated devices is contained within the American National Standard for such devices and is obtainable, for a fee, from AAMI. A summary of the features of the standard is published in the journal *Hypertension*. The BHS protocol is published in full in the *Journal of Hypertension*.

The BHS protocol has previously insisted on assessment of observers according to strict criteria before starting device validation and these recommendations have now been adopted in the revised AAMI protocol. The BHS protocol insists, moreover, that observers be carefully trained and that they be continuously assessed during the study to detect any variance between them which might be to the disadvantage of the test device.

To assess the problem of devices losing accuracy under the stress of everyday use, the BHS protocol stipulates that the laboratory validation test should take place only after the device has been in use for the purpose for which it was designed for a reasonable period of time, so that the device is tested after a trial period rather than when it is brand new. This stipulation does not apply to the AAMI protocol.

The BHS protocol does not make provision for intra-arterial comparison for two reasons. First, because the two techniques yield different values, and secondly because of ethical considerations. The AAMI protocol makes provision for intra-arterial comparison in three circumstances: (1) same-arm simultaneous comparisons for devices designed to measure blood pressure in critical care units, operating rooms, and investigative laboratories, where presumably the rationale is that the device will be required to measure intra-arterial blood pressure and that its algorithm should be designed accordingly; (2) intra-arterial comparison in neonates in whom umbilical arterial catheterization is recommended; and (3) ambulatory evaluation of 24-hour ambulatory devices using opposite-arm comparison.

In both protocols, 85 subjects with a wide range of pressure are recommended for the primary noninvasive validation test. Whereas the original BHS protocol stipulated that three paired comparisons be used individually for analysis, the original AAMI protocols recommended that the mean of three readings be used. The AAMI protocol now recommends analysis of each individual comparison giving at least 765 observations for analysis. The 765 readings are calculated using 85 subjects in 3 positions (sitting, standing, and lying) with three readings in each position.The deflation mechanisms of many automated devices are such that auscultatory comparison with the test device is often not possible. Blood pressure variation between arms may be considerable and is not necessarily constant for individual subjects, thus making opposite-arm comparison unreliable. The revised BHS protocol recommends, therefore, a sequential same-arm comparison only, whereas the AAMI protocol, though acknowledging the problems associated with simultaneous same-arm and opposite-arm comparisons, permits these tests. The AAMI protocol recommends that auscultating observers measure blood pressure to the nearest millimeter of mercury whereas the BHS recommends the nearest 2 mm Hg.

Both protocols recommend giving the mean and standard deviation between the device and the reference standard, but the AAMI protocol stipulates that this must not exceed $\pm$ 5 mm Hg and $\pm$ 8 mm Hg respectively. The BHS protocol regards this as too liberal and recommends calculating the percentages of differences falling within 5, 10, and 15 mm Hg, thus allowing grading of the test device from A (very good) to D (very poor). Similar percentage groupings are now recommended in the revised AAMI protocol. Both protocols now recommend plotting the average blood pressure against the differences between the methods for each comparison.

A modification of importance in the revised BHS protocol is that analysis of the validation data makes provision for the influence of differing blood pressure levels on device accuracy. Analysis across the pressure range, as recommended in the original protocol, may possibly mask the influence of increasing pressure on device accuracy.

The revised BHS protocol has been modified to make it more applicable to the generality of blood pressure measuring devices while continuing to incorporate special provisions for the evaluation of ambulatory systems. The revised evaluation program is now divided into two parts. The first part comprises the main validation procedure to which all blood pressure measuring devices should be subjected and consists of five phases: (1) before use device calibration; (2) in-use (field) phase; (3) after-use device calibration; (4) static device validation; and (5) report of validation. The second part provides validation procedures for special groups, such as pregnant women, the elderly, and chlidren, and device validation for special circumstances, such as 24-hour blood pressure measurement and blood pressure measurement during exercise. The validation procedures in the second part are undertaken only if a device has successfully completed all phases of the first part and achieved at least a B grading for accuracy for both systolic and diastolic blood pressure. The AAMI protocol recommends that special groups, such as the elderly, be represented in a heterogeneous population for the main validation test.

The BHS protocol recommends that all devices be assessed under the working conditions for which they were designed, including ambulatory systems. The AAMI protocol only makes this recommendation for ambulatory systems. Both protocols stipulate basic requirements for the information manual, and the BHS protocol provides, in addition, a detailed appendix listing the information requirements.

Experience with the AAMI and BHS protocols is growing. To date some 20 blood pressure measuring devices have been evaluated according to one or both of these protocols. These include seven devices for self-measurement of blood pressure, ten ambulatory devices, the Hawksley random zero sphygmomanometer, and the Dinamap 2180. Validation of blood pressure measuring systems according to these protocols has permitted prospective purchasers to examine the accuracy and performance of devices and to compare one device with another. Furthermore, the validation procedures have been used to indicate to manufacturers that their devices must meet certain minimum standards. Moreover, the protocols have provided a means of ensuring that devices being used in research have satisfied the basic criteria of the protocols. In a number of European multicenter studies, for example, ambulatory systems must have fulfilled the criteria of either the AAMI or BHS protocols before being acceptable for use in these studies. In the United States, the AAMI protocol is accepted as a national standard and in Europe, the European Community working party, CEN/TC 205/WG 10 Noninvasive Sphygmomanometers is likely to refer to existing protocols.

10.0 BLOOD PRESSURE MEASUREMENT TECHNIQUES AND TECHNICAL ISSUES

While invasive recording made directly from the artery is widely accepted as being the most accurate method (the gold standard), it is rarely used clinically outside the hospital environment. With rare exceptions, the clinical measurement of blood pressure is performed noninvasively, traditionally by an observer with a stethoscope, but increasingly by automatic or semiautomatic devices. Most of these use either the Korotkoff sound or the oscillometric techniques, although there are other methods that have recently become available.

10.1 Blood Pressure Measurement

10.1.1 Intra-Arterial Recording

The clinical use of intra-arterial blood pressure recording is limited by its invasiveness. Consequently there is virtually no prospective clinical data based on this technique. However, it is still often used for the evaluation of noninvasive blood pressure recorders. While intra-arterial recording is potentially the most accurate method for measuring blood pressure, its accuracy is limited by the frequency response of the recording system, particularly when long, thin fluid-filled lines are used to connect the artery and the transducer.[275,276] However, newer catheter-tip transducers that are small enough to be inserted in the brachial artery eliminate these problems, and also give recordings that are free of artifact. Figure 10.1 compares measurement of intra-arterial pressure made with a conventional fluid-filled system and a Millar solid-state catheter-tip transducer.

10.1.2 Noninvasive Techniques for Measuring Blood Pressure — Korotkoff Sound Technique

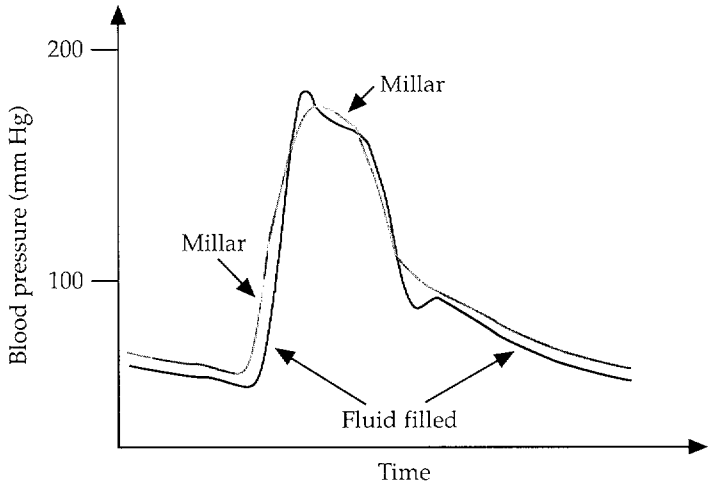
Despite continued efforts to find a superior method, the technique first described by Korotkoff in 1905 is still the most widely used.[277] The classic description of the five phases of the Korotkoff sounds was first proposed by Ettinger in 1907.[278] These phases are:

- A clear tapping sound that gradually increases in intensity
- A murmur or swishing noise of variable duration
- Murmur disappears and a clear sound increasing in intensity
- Muffling or a soft blowing quality
- Disappearance of sound.

The scientific validity of this classification is questionable, but it is still widely used.

The mechanism of the origin of the Korotkoff sounds has been a subject of debate for many years. The two most popular theories are that they are caused by pressure-induced movement of the arterial wall, or by turbulent flow through the compressed arterial lumen.[279] Both may be true.

Figure 10.1 — Intra-arterial measurements from brachial artery using both a fluid-filled catheter (—) and a Millar solid-state catheter-tip transducer (—). Note the overshoot from the fluid-filled system due to under-damping.



10.1.3 Comparisons of Auscultatory and Intra-Arterial Blood Pressure

Several studies have compared measurements taken by the auscultatory Korotkoff sound method and intra-arterial recordings. The range of discrepancies is quite striking, and the difference between the two methods may be as much as 25 mm Hg in some individuals.[280] These results show that the Korotkoff sound method tends to give values for systolic pressure that are lower than the intra-arterial pressure, and diastolic values that are higher. The discrepancies between the two methods cannot be attributed to differences in arm circumference or skinfold thickness. One factor may be the shape of the intra-arterial pressure wave. When the systolic peak is rounded, the agreement between the direct and indirect estimates of blood pressure are usually close, but when the wave is sharply peaked, the auscultatory readings tend to be too low.[281] This may be because such brief peaks of pressure may be insufficient to open the occluded artery and, hence, generate a Korotkoff sound. An alternative explanation is that such peaks are artifacts due to underdamping.

The human ear can only detect vibrations above a frequency of around 20 Hz. In fact, as shown in Figure 10.2, most of the energy that is generated under a sphygmomanometer cuff during blood pressure measurement is below the audible range, and shows no sudden change at systolic or diastolic pressure, in contrast to the more abrupt changes in energy above 20 Hz.

There is still no universal agreement as to which phase of the Korotkoff sounds should be used for recording diastolic pressure: studies in which phases IV and V have been related to intra-arterial diastolic pressure have shown no clear superiority of either phase.

The official recommendation of the American Heart Association was formerly to report both the fourth and fifth phases, but more recently to use the fifth phase, except in children.[282] Most of the large-scale clinical trials that have evaluated the benefits of treating hypertension have used the fifth phase, although the Framingham Heart study, which has given us much of our knowledge about the risks associated with hypertension, used the fourth phase. Most clinicians today use the fifth phase.

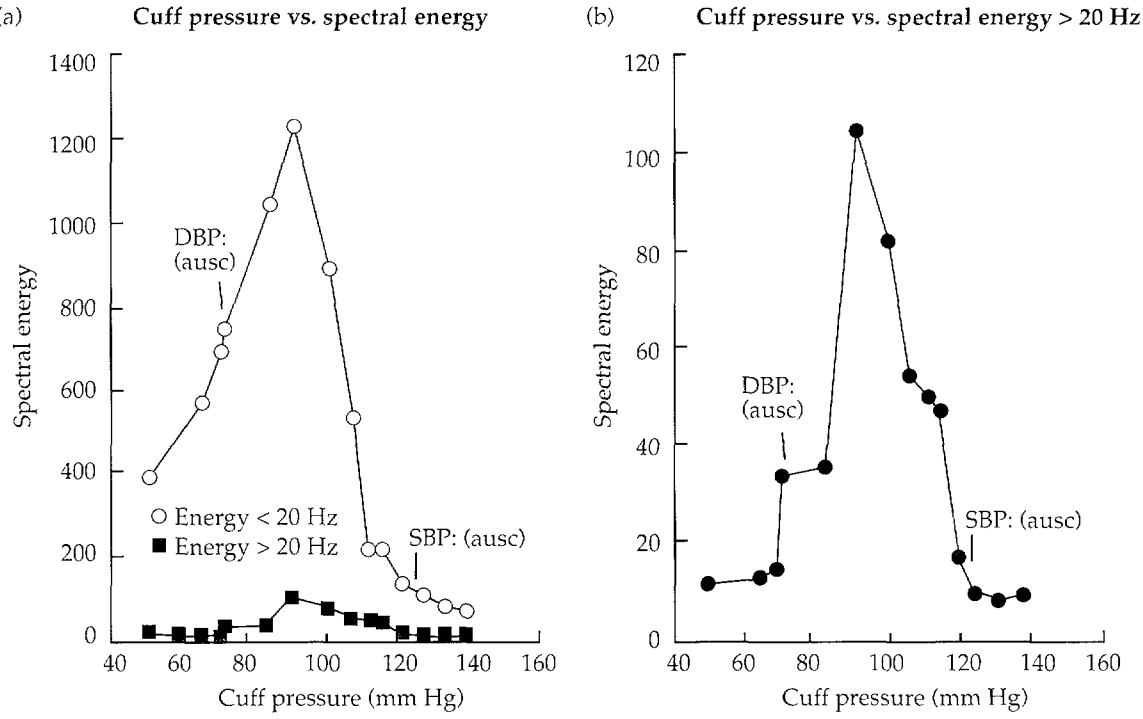
10.1.4 Sources of Error with the Auscultatory Method

A number of factors lead to inaccuracies with the Korotkoff sound technique.

10.1.4.1 Cuff Size

The size of the cuff relative to the diameter of the arm is critical. Bladder width should be at least 40% of the arm circumference. The length of the bladder should encircle at least 80% of the circumference of the arm. In the obese patient a large adult size cuff with 15 cm width (or larger) bladder should be used. Using too small of a cuff will yeild high readings.[283,284]

Figure 10.2 — Recordings obtained with a high-fidelity transducer placed under a sphygmomanometer cuff during deflation: (a) spectral energy of the signal has been separated into components above and below 20 Hz. Note that most of the energy is below this level; (b) an amplified plot of the energy above 20 Hz, corresponding to the audible Korotkoff sounds. With the oscillometric technique, low-frequency vibrations in the cuff are detected.



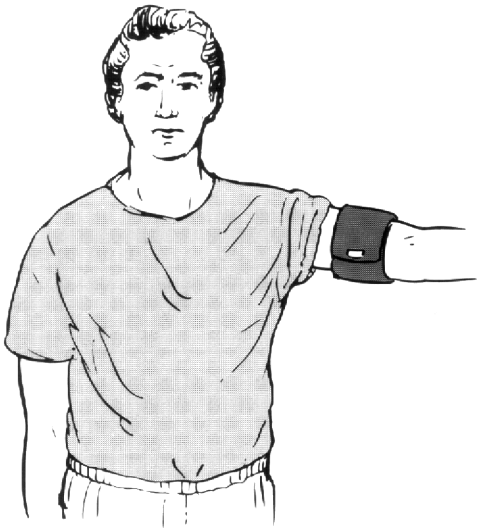
10.1.4.2 Arm Position

Blood pressure measurements are also influenced by the position of the arm. As shown in Figure 10.3, there is a progressive increase in the pressure of about 5 to 6 mm Hg as the arm is moved down. These changes are exactly what would be expected from the changes of hydrostatic pressure.[285]

These findings have important implications for ambulatory monitoring — serious errors in the recorded pressure will occur if the position of the upper arm varies while readings are being taken.[286] During the day this can be prevented by ensuring that the arm is always parallel to the trunk, but problems will occur at night when the subject is sleeping on their side. Schwan and Pavek studied subjects in four supine positions while blood pressure was being monitored from an ambulatory monitor on the left arm.[287] As shown in Figure 10.4, blood pressure was 10 mm Hg lower when lying on the right side (with the monitored arm above heart level) than when lying on the left (with the monitored arm below heart level). This observation may explain some of the variance of noninvasive blood pressure measurements seen during sleep.

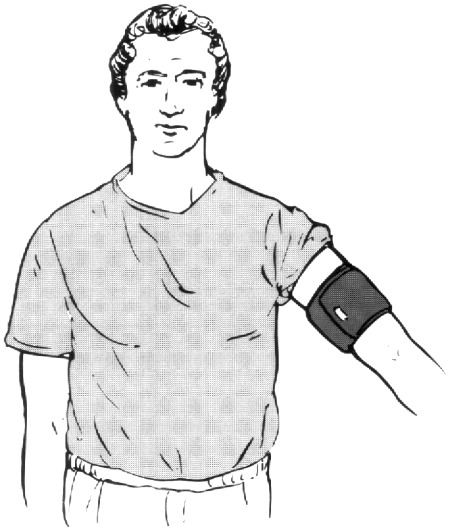
Figure 10.3 — Effects of different arm positions on blood pressure.

(a)



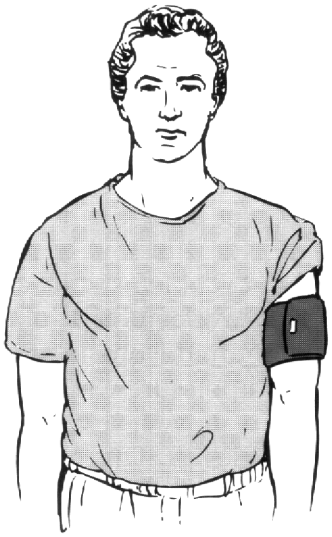
115/73 mm Hg

(b)



120/78 mm Hg

(c)



126/84 mm Hg

10.1.4.3 Observer Error and Observer Bias

Observer error and observer bias are important sources of error when conventional sphygmomanometers are used. Differences of auditory acuity between observers may lead to consistent errors, and digit preference is very common, with most observers recording a disproportionate number of readings ending in five or zero. The level of pressure that is recorded may also be profoundly influenced by behavioral factors related to the effects of the observer on the subject, the best known of which is the presence of a physician. Other factors that influence the pressure that is recorded may include both the race and sex of the observer: men tend to have higher pressures when taken by a woman than by a man, while the opposite is true for women. Whether or not the person taking the blood pressure is of the same race as the subject may also be important.

The extent to which interobserver differences in blood pressure are due to differences in technique as opposed to the white coat effect can be assessed by having two observers take simultaneous readings with a double-headed stethoscope.

10.1.4.4 Blood Pressure Variability

As the cuff is deflated, beats with a relatively high systolic pressure are more likely to be the first beats at which an audible Korotkoff sound is heard, and hence registered as the systolic pressure level. This tendency for Korotkoff sound systolic pressure to overestimate the average level will be greater when blood pressure is more variable.[288]

10.1.4.5 Rate of Cuff Inflation and Deflation

With very slow rates of deflation (2 mm Hg/second or less) the intensity of the Korotkoff sounds is diminished, resulting in slightly higher diastolic pressures. This effect has been attributed to venous congestion reducing the rate of blood flow during very slow deflation.[289] The tendency for Korotkoff sound systolic pressure to overestimate the average level discussed above is accentuated by a slow cuff deflation rate.[288] Too fast a deflation rate will underestimate systolic and overestimate diastolic pressure. The generally recommended deflation rate is 2 to 3 mm Hg/second.

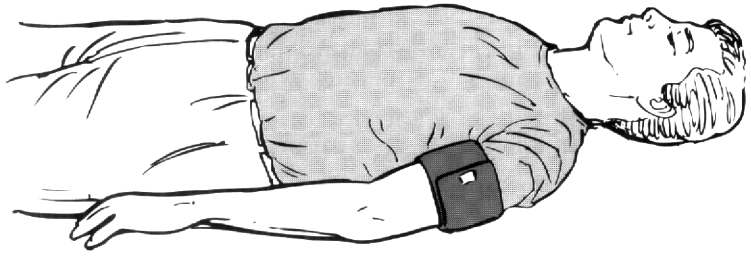
10.1.4.6 Auscultatory Gap

This phenomenon has a venerable history, having been recognized by Krylov in 1906 only a year after Korotkoff first described the auscultatory technique.[290] It can be defined as the loss and reappearance of Korotkoff sounds that occur during cuff deflation between systolic and diastolic pressures, in the absence of cardiac arrhythmias. Thus, if its presence is not recognized, it may lead to the registration of spuriously high diastolic or low systolic pressures.

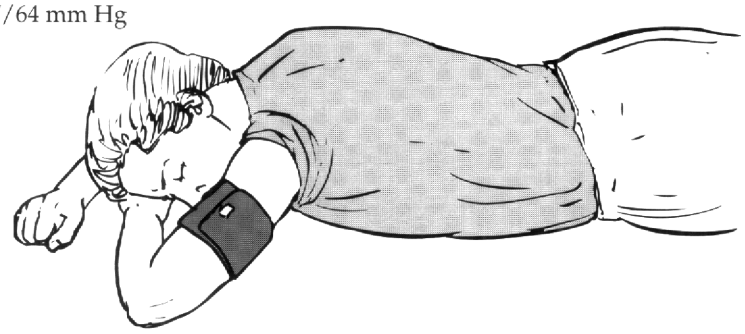
There are three types of auscultatory gap.[291] Two are due to phasic changes of arterial pressure. The most common type (G1) occurs when there is a transient decrease of blood pressure following the registration of systolic pressure, so that Korotkoff sounds are no longer heard but reappear as the pressure rises again. The mirror image of this (G2) occurs with a transient increase of pressure when the cuff is just above

Figure 10.4 — Blood pressure measurements in different positions: (a) supine, 122/67 mm Hg; (b) face down, 117/64 mm Hg; (c) on right side, 107/55 (mm Hg); and (d) on left side, 117/67 mm Hg.

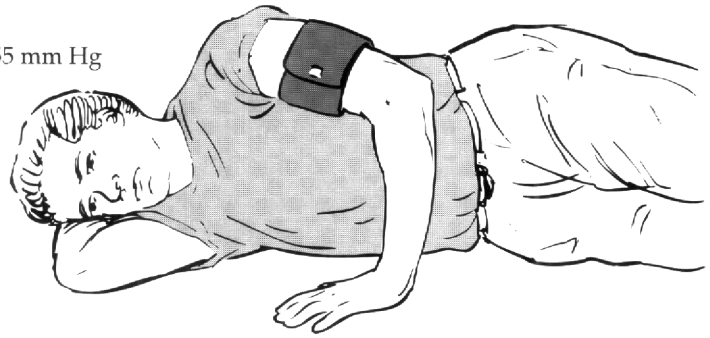
(a) 122/67 mm Hg



(b) 117/64 mm Hg



(c) 107/55 mm Hg



(d) 117/67 mm Hg



diastolic pressure. The third type (G3) is not due to any sudden change of pressure, but is seen in patients who have inherently inaudible Korotkoff sounds.

The auscultatory gap may pose a problem for automatic recorders which operate by the Korotkoff sound technique, and result in gross errors in the measurement of diastolic pressure. Oscillometric devices are less susceptible to this problem.

10.1.4.7 Technical Sources of Error

There are also technical sources of error with the auscultatory method, although these are usually much less when a mercury column is used than with many of the semiautomatic methods. They include the mercury should read zero when no pressure is applied, and should fall freely when the pressure is reduced (this may not occur if the mercury is not clear or if the pinhole connecting the mercury column to the atmosphere is blocked). With aneroid meters, it is essential that they be checked against a mercury column both at zero pressure and when pressure is applied to the cuff. Surveys of such devices used in clinical practice have shown them frequently to be inaccurate.[292]

10.1.4.8 Cuff-Inflation Hypertension

Although in most patients the act of inflating a sphygmomanometer cuff does not itself change the blood pressure, as shown by continuous blood pressure recordings, in occasional patients there may be a transient but substantial increase of up to 40 mm Hg coinciding with cuff inflation.[293] An example is shown in Figure 10.5.

This condition appears to be distinct from white coat hypertension, where the increase of pressure both precedes the act of inflation and outlasts it. It should also be distinguished from the transient increase of blood pressure which occurs during self-measurement, due to the muscular act of inflating the cuff.

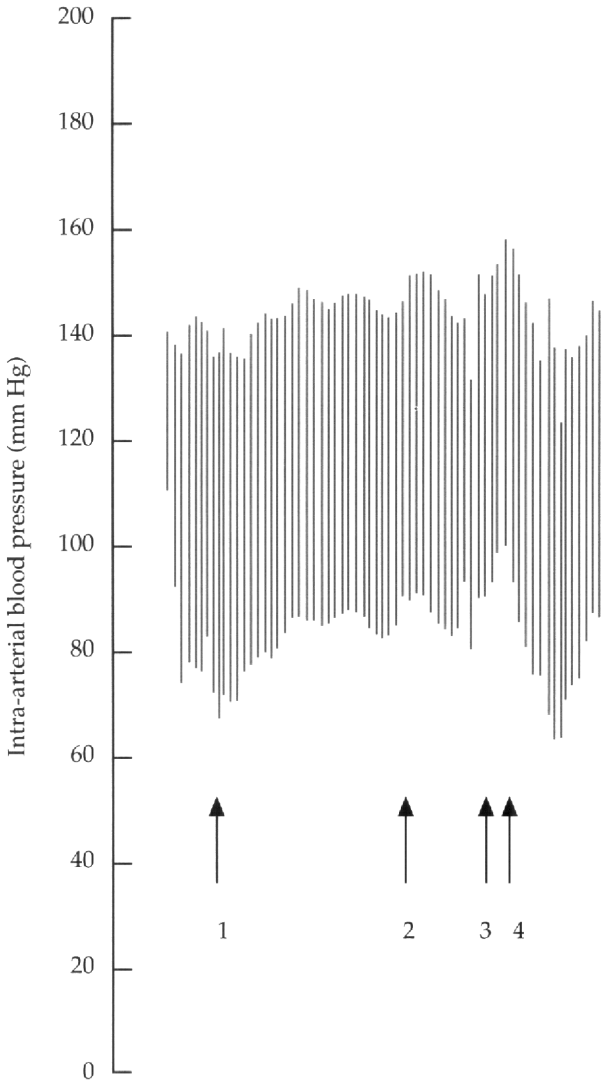
10.1.4.9 Pseudohypertension

This phenomenon has been thought to be an important source of error in elderly subjects, and results from rigidity of the brachial artery causing resistance to compression by the sphygmomanometer cuff. The indirect pressure is thereby overestimated.[294] Reports on the prevalence of this situation differ widely, but it is probably relatively uncommon.[295]

10.1.5 Oscillometric Technique

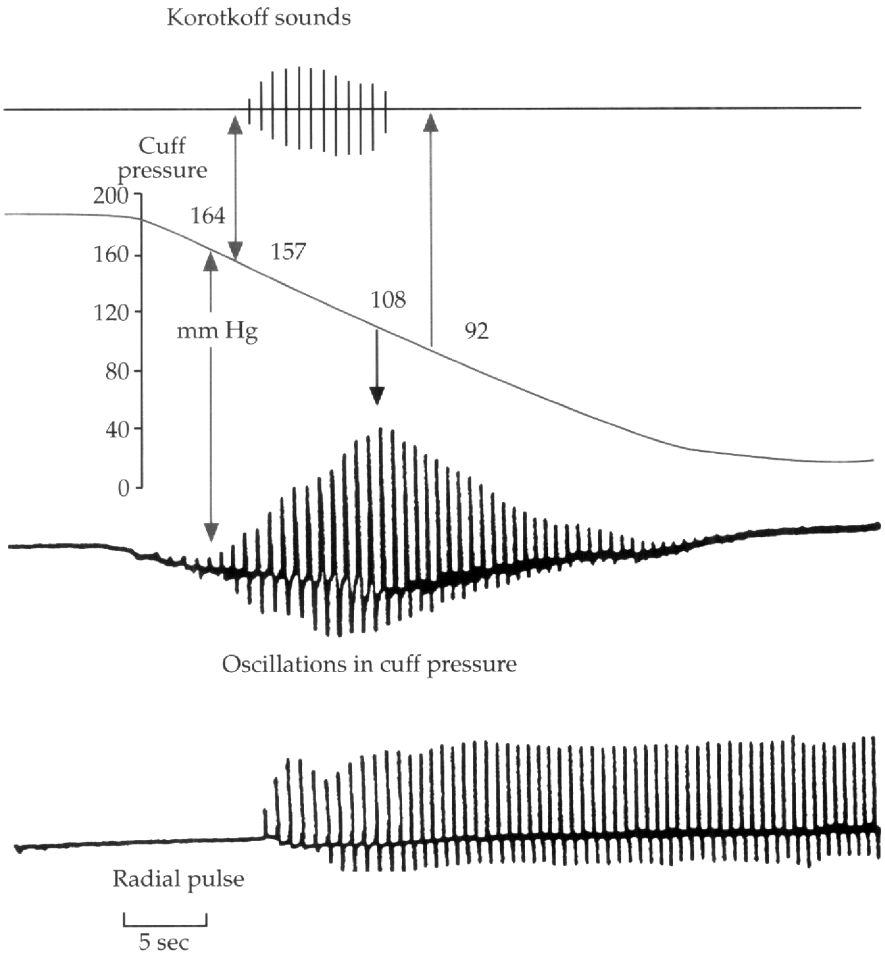
This was first demonstrated by Marey in 1876, and it was subsequently shown that when the oscillations of pressure in a sphygmomanometer cuff are recorded during gradual deflation, the point of maximal oscillation corresponds to the mean intra-arterial pressure.[296,297] The oscillations begin well above systolic pressure and continue below diastolic (see Figure 10.6). Systolic and diastolic pressures are estimated indirectly according to some empirically derived algorithm. One advantage of the method is that no transducer need be placed over the brachial artery, so that placement of the cuff is not critical. Other advantages include an absence of problems related to auscultatory

Figure 10.5 — An example of cuff-inflation hypertension with intra-arterial recording. Arrow 1 indicates start of inflation, 2 the moment systolic pressure was recorded by the observer, 3 the moment diastolic pressure was recorded, and 4 the beginning of rapid cuff deflation.



gaps and Korotkoff sounds being audible below diastolic pressure, as occurs during pregnancy. Several validation studies comparing the oscillometric technique with intra-arterial recording have confirmed its accuracy, particularly for measuring the mean arterial pressure.[298] The oscillometric technique has recently been used successfully in ABP monitors (such as the SpaceLabs Medical recorders). It should be pointed out that different brands of oscillometric recorders use different algorithms, and there is no generic oscillometric technique.

Figure 10.6 — The oscillometric technique of measuring blood pressure. Traces from top to bottom represent: Korotkoff sounds, cuff pressure, oscillations in cuff pressure, and the radial pulse. Note that the cuff oscillations do not exactly correspond to the appearance and disappearance of Korotkoff sounds.



Other potential advantages of the oscillometric method for ambulatory monitoring are that it is less susceptible to external noise (but not to low-frequency mechanical vibration), and that the cuff can be removed and replaced by the patient, for example, to take a shower. The main disadvantage of auscultatory and oscillometric is that they do not work well during physical activity, when there may be considerable movement artifact. However, the most widely validated oscillometric recorders provide better artifact rejection.

10.2 Technical Issues with Ambulatory Monitoring

10.2.1 How Many Readings are Needed?

Both the interval between successive readings and the duration of the recording can be varied, and it is important to develop some guidelines as to what constitutes an adequate recording. Subjects occasionally disconnect the recorder before the end of the full recording period, and there are often missing readings as a result of movement artifact, etc.

Statistical analysis of data obtained with ambulatory monitors indicates that five or six readings would give an adequate representation of the average pressure in a particular setting such as at work or at home.[299] Thus, a sampling frequency of one reading every 30 to 60 minutes may be adequate to describe the average levels in different settings, but more frequent readings would be needed to describe short-term variability of blood pressure.[299,300]

A generally accepted recommendation is for a minimum of eight hours (or 30 readings) for an adequate daytime recording, and at least three hours (or six readings) during sleep.

10.2.2 Reliability of Ambulatory Recordings

One of the rationales for making ambulatory recordings is that they will be more representative of an individual's true pressure than clinic measurements. A potential disadvantage is that there may be considerable variation in the individual's activities from one occasion to another. Therefore, it is of considerable importance to know how reliable (reproducible) such measurements are.

A large number of studies on the reproducibility of ABP measurement have been published, with intervals between the two recordings ranging from one day to six months.[301] None of the studies showed any significant difference between the average ambulatory pressures recorded on the two occasions over the short-term (less than six months). The study with the longest interval (six months) found a significant decrease of systolic pressure on the second occasion, but no change of diastolic pressure.[302] The finding of no consistent difference between recordings made on successive occasions does not in itself imply that there is good reliability, but merely that there is no major order effect. However, the correlation coefficients between the two sets of readings have ranged between 0.72 and 0.93 for systolic pressure, and 0.53 and 0.87 for diastolic pressure, indicating that the reliability is acceptable, and that a single recording can characterize an individual's average ABP in the circumstance in which the recording was made.

In contrast to the high reliability of the average levels of pressure, the within-subject variability of pressure (measured as the standard deviation or the coefficient of variation) shows poor reliability, although it can be improved if steps are taken to reduce the random error, e.g., by matching for equal numbers of readings on the two occasions, or by controlling the subject's activities on the two occasions.

In marked contrast to the high level of reliability seen when the subject's activities remain the same on the two recording days, the blood pressure may be substantially lower on a nonwork day than on a work day.[303]

10.2.3 Elderly Subjects

In some older people there is an increase of systolic pressure without a corresponding increase of diastolic pressure (systolic hypertension), which has been attributed to a diminished distensibility of the arteries with increasing age. In extreme cases this may result in a diminished compressibility of the artery by the sphygmomanometer cuff, so that falsely high readings may be recorded — often referred to as pseudohypertension of the elderly.[304] In such patients, vascular calcification may, in some patients, be seen on a plain x-ray. It has been suggested that a positive Osler maneuver may help to identify such patients, but it has not proved to be very reliable.[305] This maneuver is performed by inflating a sphygmomanometer cuff to above systolic pressure; if the brachial or radial artery is still palpable the maneuver is said to be positive. The best noninvasive method for detecting pseudohypertension is to use a finger cuff method such as the Finapres device; but oscillometric measurement from the brachial artery may also be superior to Korotkoff sound measurement.[306]

10.2.4 Obese Subjects

It is well known that the accurate estimation of blood pressure using the auscultatory method requires an appropriate match between cuff size and arm diameter. In obese subjects, the regular adult cuff (12 x 23 cm) may seriously overestimate blood pressure.[307] The British Hypertension Society recommends a bladder length of 42 cm for obese arms.[308] Note: Width is more important than length.

10.2.5 Exercise

During dynamic exercise the auscultatory method may underestimate systolic pressure by up to 15 mm Hg, while during recovery it may be overestimated by 30 mm Hg.[309] Errors in diastolic pressure are unlikely to be as large, except during the recovery period, when falsely low readings may be recorded. This is why the American Heart Association recommends taking the fourth phase of the Korotkoff sound after exercise.

11.0 ANALYSIS OF AMBULATORY BLOOD PRESSURE DATA

A single ambulatory blood pressure (ABP) recording can produce up to 100 readings of blood pressure per subject. A discussion of how they should be used and analyzed follows.

Ambulatory recordings offer several advantages over clinic measurements. First, because so many readings are taken, ambulatory monitoring gives a more precise estimate of a subject's true level of blood pressure and its variability. Second, readings can be taken in a wide variety of settings. And third, the readings are less likely to be confounded by factors such as observer error and the white coat effect. However, the very nature of ambulatory monitoring means that the situations in which blood pressure readings are made are much less controlled than with clinic measurements. This presents both a problem and an opportunity. The problem is that it becomes much more difficult to compare the data obtained from one recording with that of another,

because the circumstances of the recording are unlikely to be identical for each individual, and the total number of readings is also likely to vary. These factors need to be taken into consideration when the data is analyzed and interpreted. The opportunity is that ambulatory monitoring enables quantitative study of the influences of these same factors on blood pressure.

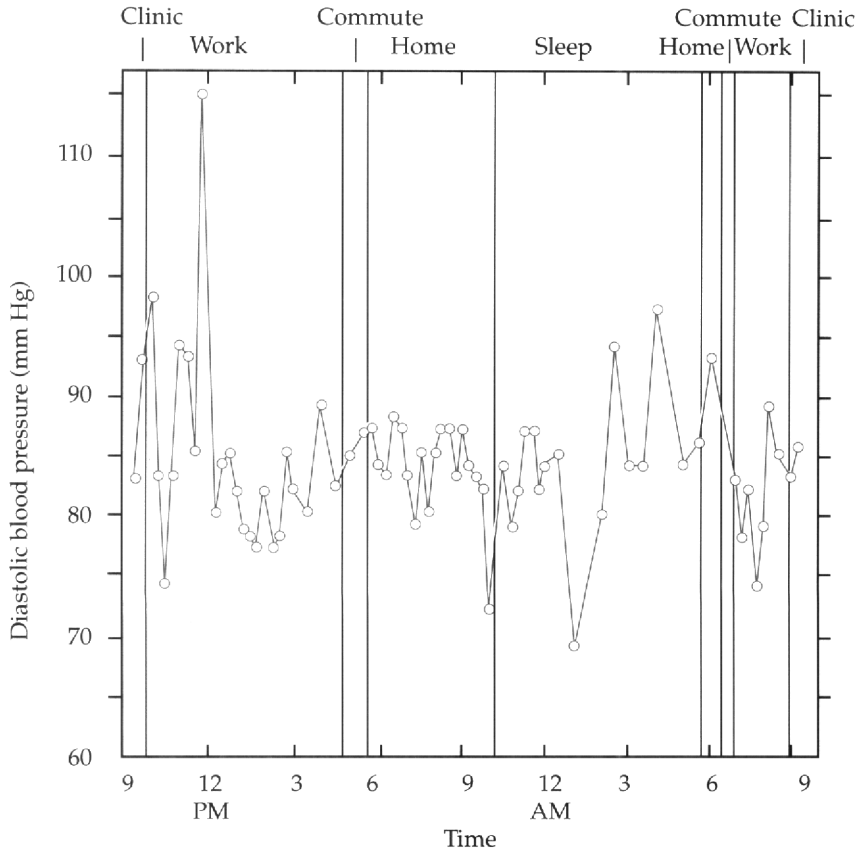
While issues that may be important are discussed, and suggestions for analyses proposed, it must be stressed that no single method is appropriate to answer all research questions, and furthermore, we would expect all reasonable approaches to arrive at similar conclusions. Finally, the analytical problems for ABP data are so complex that it is most unlikely that any single analytical approach will answer all potential questions.

11.1 Data Editing and Reliability

11.1.1 Data Editing and Outlier Detection

All ambulatory recordings include a certain number of readings that are much higher or much lower than the majority. This raises the question as to whether these readings are simply outliers, or whether they are artifacts caused either by equipment malfunction or by movement of the subject. If they are artifacts, their inclusion may

Figure 11.1 — A 24-hour recording showing diastolic pressure values in one subject. Note the outliers at 12:00 p.m. and 1:00 a.m.



have a disproportionate effect on measures of blood pressure variability, and also on measures of centrality, especially if the number of artifacts is large relative to the number of true readings.

A typical, but not ideal, example of a 24-hour blood pressure recording is shown in Figure 11.1. While most of the readings lie between 80 and 90 mm Hg, there is one clearly high reading while the subject was at work, and one quite low one during sleep. It is clearly impossible to decide retrospectively with any certainty which readings are artifacts, but a number of techniques have been used. Perhaps the most common is subjective assessment, whereby the technician or investigator scans the series of readings and picks out those that look suspicious. This can be done using a number of criteria, such as an unphysiologically narrow pulse pressure, disparity with previous readings, or incongruence with the time of day or activity. This method is theoretically unsatisfactory because it is inconsistent and subject to the biases of individual researchers, but it is nonetheless widely used.

The alternative is to use a rigorous set of rules that can be built into a computer algorithm. The simplest method is to eliminate readings which are physiologically improbable. An example is one currently incorporated into the SpaceLabs Medical software system. It identifies readings as artifactual if any of the following criteria are met:

- Systolic pressure is below 70 mm Hg or above 260 mm Hg
- Diastolic pressure is below 40 mm Hg or above 150 mm Hg
- Pulse pressure (systolic minus diastolic) is greater than 150 mm Hg or less than 20 mm Hg.

It is certainly possible for physiological levels to exceed these criteria, but in the majority of subjects most of the readings which are excluded by this algorithm are probably artifacts. However, in some normotensive subjects (e.g., young women) the blood pressure during sleep may be lower than 70/40 mm Hg at times, and it may be appropriate to reinstate readings identified as errors by the computer.

Another technique is to use an algorithm based on an empirically observed relationship between systolic and diastolic pressure which is designed to exclude readings where the pulse pressure is too narrow (e.g., 140/120 mm Hg).

Another approach, which may be used in conjunction with the algorithms described above, is to identify those readings which are out of line with the bulk of the data. The criteria here are thus relative rather than absolute. Two ways of defining such outliers have been employed. The first method is one that Clark et al. described, and identifies readings which are extreme relative to the other readings in the series.[310] This method is based on the relationship between systolic and diastolic pressure. It is possible to construct an ellipse which will include a desired percentage of readings (e.g., 95%), so that the 5% of readings lying outside the boundary of the ellipse can be identified as outliers. It is not clear whether this method is any better at detecting artifacts than any other, and it has not been used in clinical practice.

The second method is to label readings as outliers if they have a disproportionately large influence on the estimation of the effect of interest. For example, there might be a single reading whose elimination would have a major effect on the estimate of mean blood pressure. Marler et al. used an algorithm called the DFFITS statistic to identify readings which were particularly influential, and excluded these from some sets of analyses.[311] Numerous other algorithms have been described for identifying outliers and influential observations.

11.1.2 How Much Data Editing Should be Used?

One can never be absolutely sure whether an individual reading is an artifact or not. Elimination of artifacts and outliers has both benefits and costs. The extent to which it should be applied may vary from one study to another, depending on issues like the nature of the population being studied, the statistical procedures which will be used to analyze the data, the estimates or parameters to be derived, and other considerations.

Most investigators agree that the algorithms which detect physiologically improbable readings in most commercially available software packages are appropriate in the majority of cases. Such readings not only have a high probability of being truly artifactual, but also will have a large biasing effect on the summary statistics used to describe the data.

Readings which are not automatically eliminated, but are labelled as suspicious by one of the outlier detection methods described above, are less likely to be extreme, less likely to be artifactual, and less likely to have a major biasing effect on the summary statistics. The effect of elimination of such outliers is to create a set of remaining readings which are more similar to each other, that is, with a lower variance. While this similarity will tend to give a more precise estimate of the effect of interest, this apparent precision may give a false sense of security if nonartifactual readings are eliminated. Furthermore, these outliers are potentially the most important data points, if they are genuine readings.

The dangers of excessive data editing were well illustrated in a comparison of the effects of ten different published methods of data editing applied to a large data set of ambulatory recordings, most of which rejected readings with an excessively small pulse pressure.[312] These different methods had very different effects, rejecting from 1 to 17% of the total readings. Since it is not at all clear which of these methods is superior, the best policy would appear to be to keep editing to a minimum.

11.1.3 Test Theory, Reliability and Generalizability

The concept of reliability is an important one for the analysis of ABP data. It is defined as the proportion of variance in a measure that is attributable to true variability as opposed to measurement error. Such errors may be random or nonrandom; the latter are discussed in Section 11.1.4. Estimates of reliability can be obtained by using formula derived from classical test theory.[313]

One of the predictions of reliability theory is that when the reliability of a particular measure is low, the relationships between that measure and any other are also likely to be low. One solution to the reliability problem is to obtain more measurements. This, of course, can be done with ambulatory monitors. While any single reading taken by a monitor may be less reliable than a single casual measurement, the greater number of readings that can be obtained means that monitoring should provide a more reliable summary measure than casual measurement.[314]

11.1.4 Nonrandom Sources of Measurement Error

Each blood pressure measurement is subject to a certain degree of error, some of which is nonrandom. One example of this was provided by a validation study of the

SpaceLabs Medical 90207 ambulatory recorder, where it was found that the combination of being young and female was associated with a tendency for the recorder to slightly overestimate blood pressure, which was not apparent in older or male subjects.[315] Another example is exercise; while most ambulatory monitors give reliable readings at rest, errors tend to be much greater during exercise.

Clearly, these types of errors may introduce a significant bias in the estimates of the effects of situational variables on blood pressure, and in the comparisons of blood pressure between groups.

11.2 Measures of Level

Since the time that ambulatory monitoring was first introduced, estimation of the average or mean level of blood pressure has been the most widely used method of describing the data. This can be done over varying time periods — e.g., four hours, during the waking hours, over 24 hours — or according to situational variables (e.g., work and home) and enables the comparison of levels in previously defined groups (e.g., normotensives vs. hypertensives, and blacks vs. whites).

11.2.1 Mean or Median?

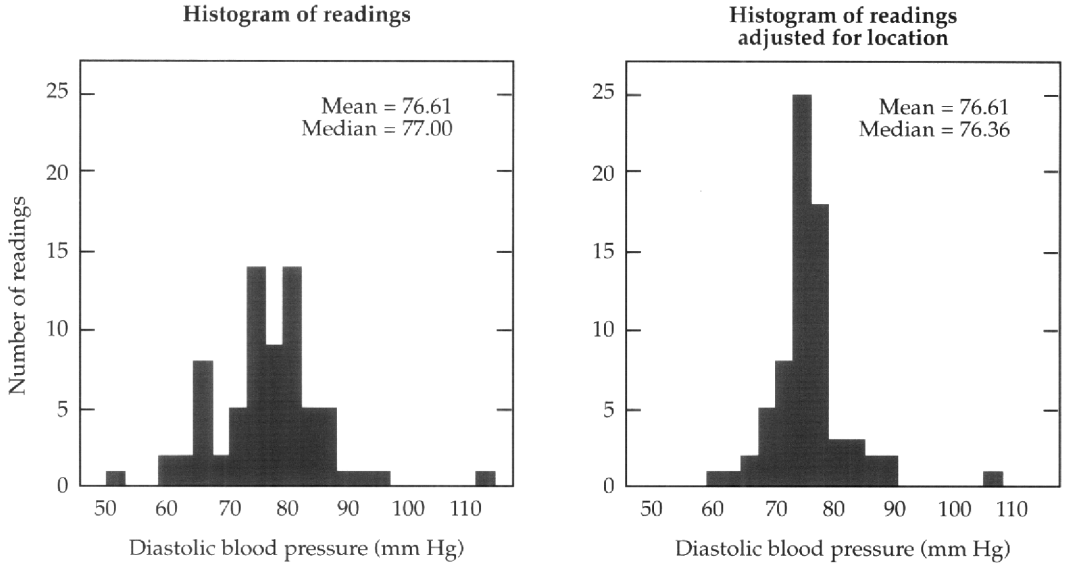
While the overwhelming majority of reports of ABP data have used the arithmetical mean to describe the level of pressure for any given situation, a case could be made for using the median value instead. Unlike the mean, the median is a nonparametric statistic and has the advantage of being influenced less by outliers at one or the other extreme of the range of values. If the data is highly skewed, the median will be closer to the center or peak of the distribution curve than the mean. However, blood pressure data is usually only slightly skewed (towards the higher readings), so that the mean and median are likely to be very close, as seen in Figure 11.2 which shows the data from Figure 11.1 replotted as histograms with and without adjustment for location.

The use of the mean, rather than the median, is generally recommended for several reasons. First, most of the available data is expressed as mean values; second, more statistical procedures are based on the use of means; and third, statistical theory has shown that the estimate of a measure of centrality is more efficient using the mean (i.e., it is more precise and has a lower variance), as long as the data is normally distributed.

11.2.2 Area Under the Curve

The area under the curve (AUC) measure has gained some adherents, both for expressing the average level of ABP, and for defining the effects of antihypertensive medication.[316] In a plot of blood pressure against time, the AUC is the area enclosed by lines joining successive data points at the beginning and end of the measurement period, and the lines joining the first and last points to the x axis (0 blood pressure). This approach is conceptually appealing as a measure of the overall burden or load of blood pressure. As a general rule, it will give values that are very close to the average level, but the correspondence will not be exact. Two individuals with the same average blood pressure but different variability will have different AUCs, with the more labile individual probably showing a smaller AUC.

Figure 11.2 — Data from Figure 11.1 replotted as histograms. Left panel: unadjusted data. Right panel: adjusted for location. Note that in each case the distribution is approximately normal, and that the mean and median values are very similar.



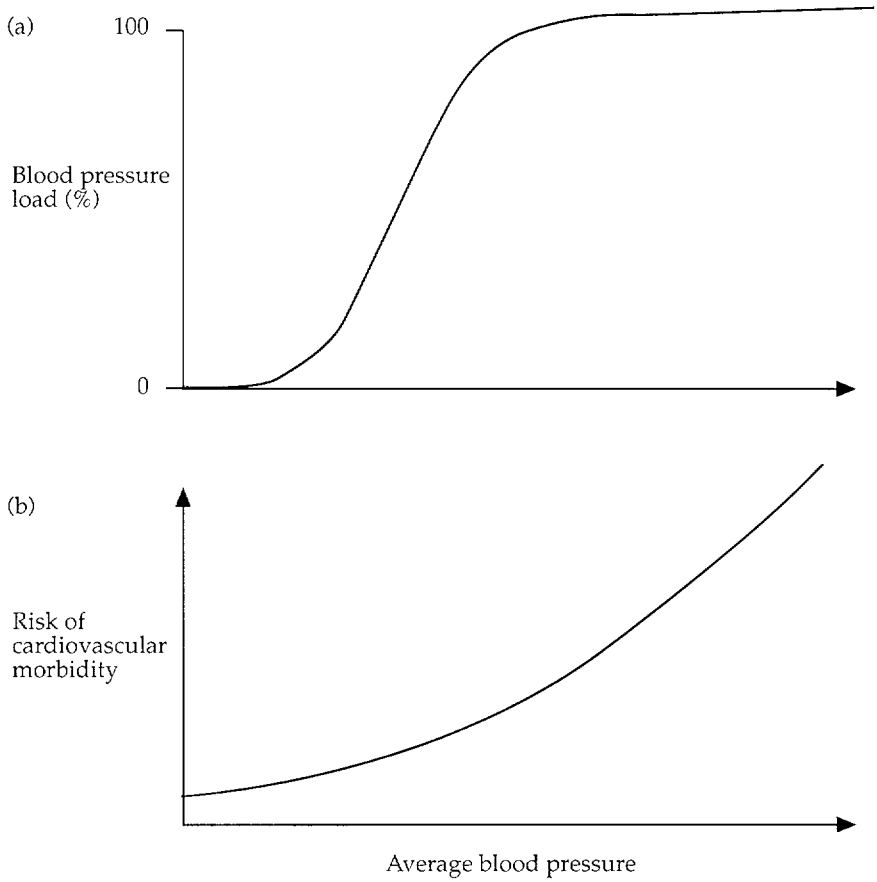
A potential advantage of the AUC is that when the interval between readings increases (e.g., because of missing data), these readings are weighted more than readings separated by shorter intervals. In contrast, the simple average does not incorporate any such time weighting.

The AUC suffers from many of the same problems as the mean. If there are periods during the recording where the error rate is high (e.g., from movement artifact) those readings that remain will have a disproportionately large influence on the AUC, and if they too are erroneous, may introduce a significant bias. Its use is not recommended because it is influenced both by the mean level and by the variability of blood pressure, and it may be preferable to analyze these two components separately.

11.2.3 Blood Pressure Load

The blood pressure load is expressed as the percentage of readings above a fixed threshold level, typically 140/90 mm Hg or 140/90 mm Hg during the day, and 120/80 mm Hg at night.[317,318] The estimate of load will be very much influenced by the policy adopted for editing extreme values, and if the number of readings is relatively small, the variance of the estimate of the percentage of readings above the threshold level will be much greater than for the estimate of the mean level. In other words, load is likely to be a less reliable measure than the mean. Although it has been claimed that the load correlates more closely than the average pressure with measures of target organ damage, it is likely that this will be true only over a relatively narrow range of blood pressure, for reasons given below.[318]

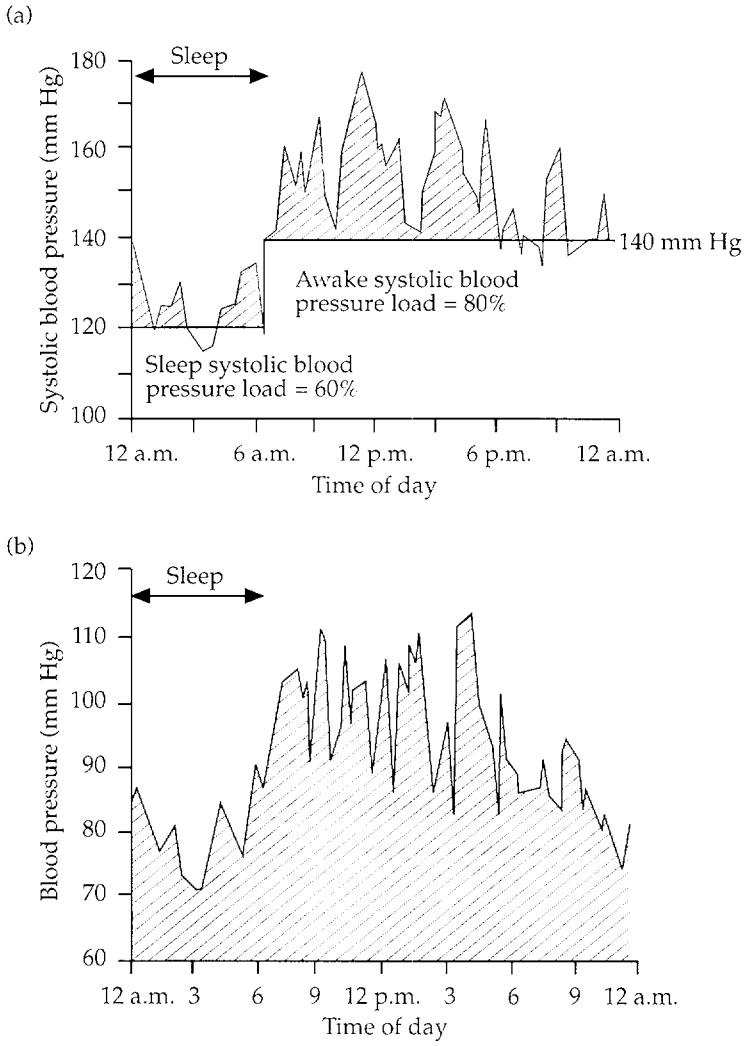
Figure 11.3 — (a) Hypothetical relationship between average blood pressure and blood pressure load; and (b) between blood pressure and its consequences.



The conceptual problem is illustrated in Figure 11.3, which shows the relationship between blood pressure load and the average (true) blood pressure. The fact that the relationship is sigmoid means that above a certain level of average blood pressure the load plateaus at 100%. It seems most unlikely that the relationships between blood pressure and its consequences (i.e., strokes, heart attacks) are of this sort, and indeed all the evidence points to the opposite view, namely that the relationship becomes steeper rather than flatter at the highest levels of pressure, as shown in Figure 11.3.[319] Furthermore, the relationship between load and average pressure depends on the threshold value which is used to define the load, the choice of which is quite arbitrary. Thus, there is no convincing evidence that any sudden increase of risk occurs above a blood pressure of 140/90 mm Hg. Another argument against the use of blood pressure load is one that its advocates might use in its support — namely that it is influenced both by the average level and by the variability of blood pressure. If one is interested in deciding which of these two components is more important it is essential to analyze them separately.

A refinement of this method incorporates two measures (AUC and load), and estimates the area under the curve above the threshold level used to define the blood pressure load, as shown in Figure 11.4.[320]

Figure 11.4 — Two methods of analyzing the overall level of blood pressure over 24 hours: (a) as blood pressure load (the percent readings above 140 mm Hg during the day and 120 mm Hg during sleep); and (b) as the AUC above the threshold level (shown as the hatched areas).



11.2.4 Estimates of Mean Levels According to Activity

An alternative method of analysis is based on activity or location, rather than on a fixed period of time. This type of analysis obviously depends on accurate diaries being kept by the subjects. Data is analyzed according to whether the subject is at work, at home, or asleep, on the grounds that activity is a more important determinant of blood pressure than time of day.[321]

Ambulatory monitoring is normally performed in free-ranging subjects, whose activities will almost certainly show significant between-subject differences. If these differences are very large, they will introduce a significant bias in the overall mean level

of blood pressure. A prime example of this would be comparison of data from one subject studied on a work day, and another studied on a nonwork day. This confounding factor is equally important for within-subject comparisons. An example of this would be a study assessing the effects of an antihypertensive medication, in which the same subjects are monitored on and off medication. Activity should, as far as possible, be held constant from one occasion to another to minimize the potential confounding of the effects of the medication from changes of activity between occasions.

When examining the effects of situational variables on blood pressure in a group of subjects it is important to adjust for individual differences in baseline blood pressure.[322] If, for example, the effects of smoking and watching television are being compared, this adjustment will distinguish between the transient effects of smoking on blood pressure and a generally higher mean blood pressure in smokers as compared to nonsmokers. An important consideration is what pressure should be taken as the baseline. One measure that has been frequently used is the calibration readings taken at the start of the ambulatory recording. While this has the advantage of being taken under highly standardized conditions, it has the disadvantage that it may not be very representative of the individual's true blood pressure. An alternative is to take the average waking pressure, which avoids this problem, but is itself influenced by the effects of the situational variables of interest.

Another question which should be addressed is whether the readings which define the blood pressure for any specific activity are consecutive. If, for example, the pressure at work is being estimated, this is nearly always the case. However, if the pressure during telephoning is of interest, there may be several periods during the day when such readings are available, but they are likely to be interspersed with other activities. The same applies to home readings which may include two distinct periods, the early morning and the evening, which are likely to be characterized by different activities and blood pressures.

It is customary to change the frequency of readings during the night, for example to take readings every 15 minutes during the day and every 30 minutes at night. If the interval between readings varies in this way, the level of blood pressure at night will be under-represented if the simple 24-hour average is computed. Therefore, a time-weighted average level is more appropriate.

The level of blood pressure for any location or activity is likely to be confounded by other cofactors. For example, we are more likely to be standing while at work than at home, and most of the readings taken lying down will be during sleep. Therefore, the apparent difference between work and home blood pressure could be due to the effects of changes of posture, rather than of work itself.[323] To address this problem, several strategies have been used. One common technique is to study the effects of each location for each level of the confounding variables. For example, one can calculate the average blood pressure level for each location (at work and at home) separately for two positions (seated and standing), and conclude that the effects of posture accounted for more of the overall variance of blood pressure than the effects of location. The obvious problem with this strategy is that the number of possible confounding variables must be small, otherwise the number of combinations of activities, postures, and locations could easily become too unwieldy. An alternative strategy is to derive estimates of the effects of activities and other variables by statistically controlling for the effects of potential confounders. This can be done by using regression techniques to estimate the effects of location while controlling for differences in posture.

11.2.5 Potential Problems with the Use of Mean Values

While the calculation of a summary measure, such as the mean, is a standard procedure and is usually the measure of choice, it is not without its problems. In particular, it may lead to biased results in some conditions, and may not necessarily be the most efficient measure. Some of the more important problems are considered below.

11.2.6 Cofactors and Multicollinearity

Many of the variables of interest are likely to be highly correlated with each other, and this needs to be taken into account when performing the analyses. In the present context this applies both to the independent variables (the situational factors) and to the dependent variables (the different measures of blood pressure). Thus, sleeping and reclining are obviously closely related with each other. In statistical terms, what will happen is that when multiple regression analysis is performed with correlated variables, the regression coefficients will have unduly large standard errors.

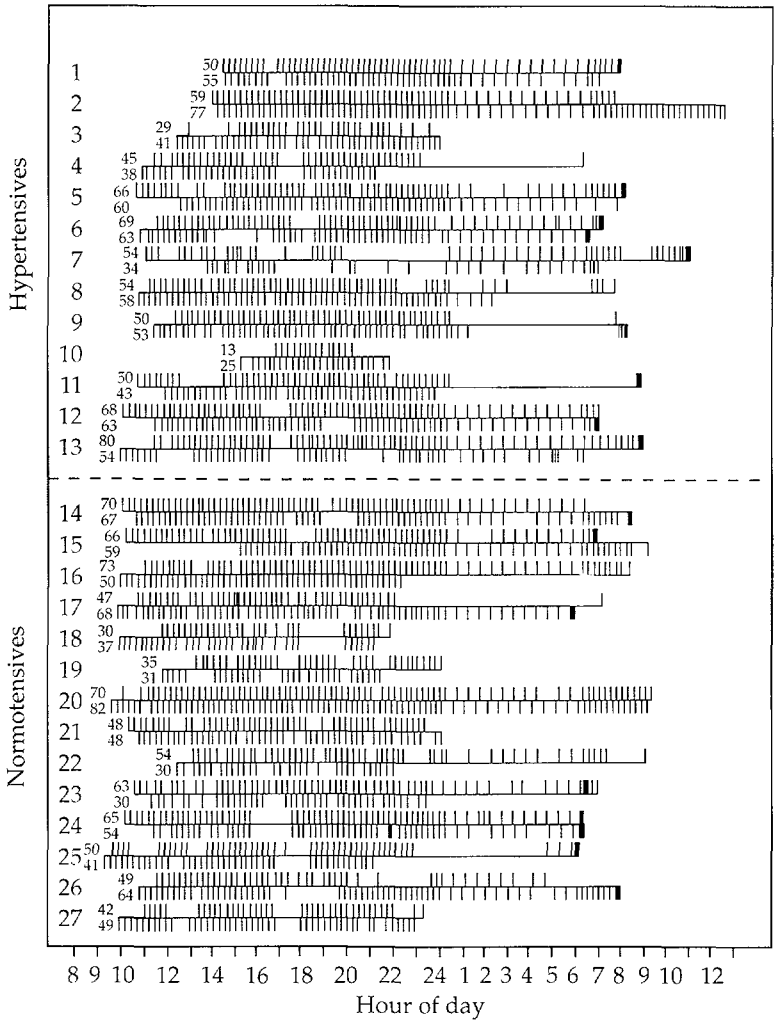
If the research question involves the calculation of some summary measure for one of the sources of variation, it is essential to control for the confounding effect of the other sources by either statistical or experimental means. This point can also be illustrated by the example of the higher blood pressure recorded at work than at home, which has often been attributed to the higher level of stress at work. An alternative explanation is that people are standing for a greater proportion of the time at work than at home, and that the higher pressure is merely a consequence of this. Certainly, changes of posture do have a major influence on ABP.

11.2.7 Variation in the Numbers of Readings

In any field study using ambulatory monitoring, it is likely that the numbers of readings for any activity will vary considerably from one individual to another, and different individuals may have quite different activities.[324] As noted above, failure to allow for these differences may affect the estimate of the average 24-hour blood pressure. The problem of comparing ABP recordings made in different subjects, and even in the same subject on different occasions, are emphasized by Figure 11.5 which shows the timing of readings made in 27 subjects (13 hypertensives and 14 normotensives), all studied on two separate days according to the same protocol, with readings taken every 15 minutes during the day and every 30 minutes at night.[324]

Both factors (the number and the variability of readings) will affect the precision with which mean levels of blood pressure can be estimated. If the purpose of the research is to estimate the population value for a group of subjects, the precision of the estimate can be improved by incorporating these two factors into the summary estimation procedure.

Figure 11.5 — Plot showing the timing of ambulatory blood pressure readings in 27 subjects (13 hypertensives and 14 normotensives), each of whom was monitored on 2 days. The readings for day 1 are plotted as vertical bars above the horizontal line, and those for day 2 below. The number of readings for each of the days is shown at the beginning of the line.



11.3 Measures of Variability

The term blood pressure variability encompasses a number of sources of variability with different physiological mechanisms and time courses. The short-term variability that is associated with respiration and Mayer waves can only be evaluated by beat-to-beat measurement of blood pressure, and, with intermittent blood pressure sampling, merely serves as a source of random error. With sampling every 15 minutes, the main source of variability is likely to be changes of respiration, physical and mental activity. The overall level of variability will be determined by two factors — the frequency and intensity of different activities on the one hand, and blood pressure reactivity to these different stimuli on the other. For research purposes it may be important to separate the

relative contributions of these two factors. In principle, this could be done statistically or experimentally. For the former, variability would be standardized for changes in the levels of situational variables (posture, location, activity, etc.), while the latter could involve putting subjects through a standardized protocol, such as is done for reactivity testing in the laboratory, but has so far rarely been done using ambulatory monitoring.

11.3.1 Absolute or Relative Measures of Variability

An important question is whether variability should be expressed in absolute terms (e.g., as the standard deviation) or in relative terms (e.g., as the coefficient of variation). Within-subject short-term variability (measured over 1/2-hour intervals with intra-arterial monitoring) increases as the average level of blood pressure increases, regardless of whether it is expressed in absolute or in relative terms.[325] On the other hand, comparison of variability between subjects (normotensives vs. hypertensives) shows that it is higher in absolute terms at higher levels of pressure, but not in relative terms.

It is generally preferable to use absolute measures of variability because they keep variability and level of blood pressure distinct from each other. If, for example, we want to determine whether blood pressure level or variability is a more potent predictor of cardiovascular morbidity, we might get a very similar estimate of risk using level and relative variability of pressure, because the latter measure incorporates level. Given the fact that variability is not independent of the average level, what we really want to know is whether variability adds anything to the prediction of outcome over and above the mean level (i.e., controlling for mean level). This can best be done by using an absolute measure of variability.

Thus, for any investigation comparing the variability and level of pressure it is first appropriate to analyze the relationship between the two, and then to relate variability to the outcome measure after controlling for level. This would apply not only when blood pressure is the independent variable (as in the example quoted above), but also when it is the dependent variable, e.g., in an analysis of the effects of antihypertensive treatment on the level and variability of blood pressure.

11.3.2 Which Measure of Variability Should be Used?

There are several possible measures for expressing blood pressure variability. The standard deviation has been most widely used, and is a valid measure if the data is normally distributed, which is usually true for blood pressure. It has the additional advantage of being measured in the same units as the mean (mm Hg) whereas the variance (another possible measure) is expressed as mm Hg^2.

An important point to stress is that outliers in the data will have a much greater effect on the variance or standard deviation than on the mean because they are derived from the square of the differences of individual readings from the mean. Further, extreme positive and negative outliers will balance each other out for the estimate of the mean level, but will have the opposite effect for the estimate of variability. Since such outliers are quite likely to be artifactual readings, we should be sure that artifacts are eliminated from the data. The problem here is that we can never know which values are artifacts and which are true but extreme readings.

A way out of this dilemma is to use nonparametric measures of variability, such as the interquartile range, which are less susceptible to the influence of outliers. This type of measure has been used relatively infrequently, but is valid, and particularly useful where there are outliers and artifacts.

Another measure is the root of the mean squared successive differences (RMSSD).[326] The crucial difference from other measures of variability is that it takes into consideration the time sequence of the readings. Figure 11.6 shows three examples of hypothetical data which have the same mean and standard deviation, but different variabilities. This would be revealed by the RMSSD, which is 1.15 for example 1, 0.43 for example 2, and 5 for example 3. The RMSSD is thus useful in situations where short-term blood pressure variability needs to be distinguished from a trend or step-change in blood pressure. When variability is expressed over shorter periods, or for a situational variable (e.g., at work) the RMSSD would not have any advantage over the standard deviation.

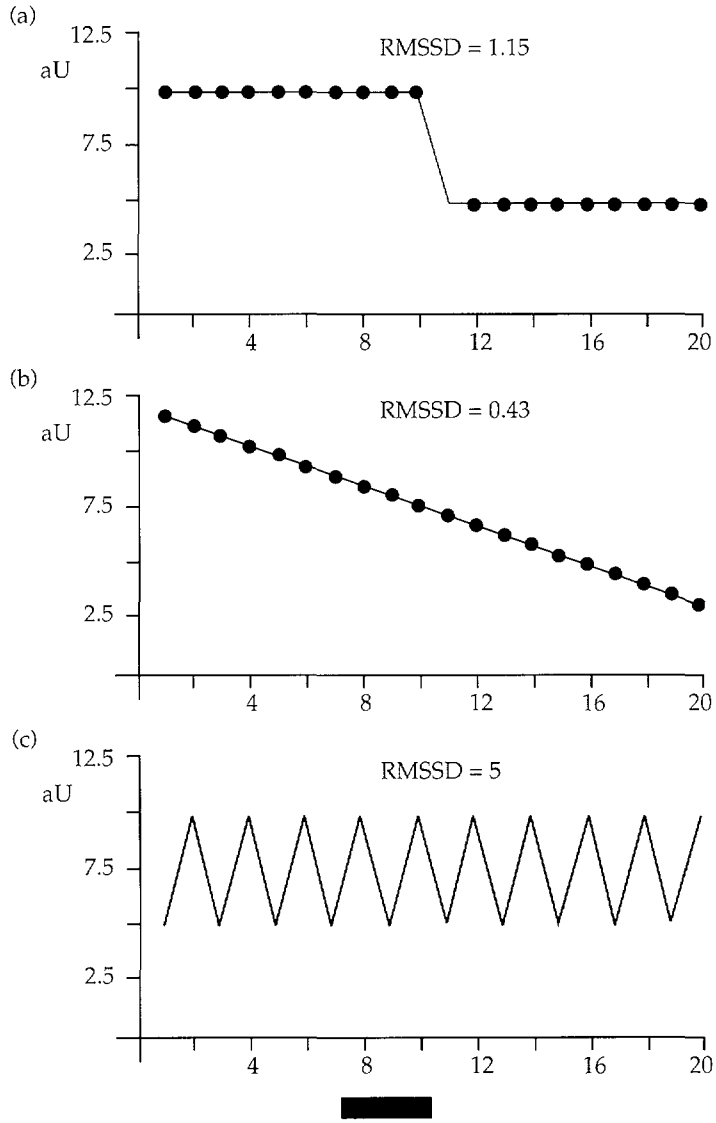


Figure 11.6 — Three hypothetical series of data points which have the same mean and standard deviation (2.5 arbitrary units or 2.5 aU). The RMSSD shows the difference in the pattern of variations: (a) 1.15; (b) 0.43; and (c) 5.0.

11.3.3 Conditional Measures of Variability

In most ambulatory studies the variability of blood pressure will be determined by two factors — behavioral (variations of activity during the recording), and nonbehavioral (the individual's intrinsic blood pressure lability). As with mean level of blood pressure, it may be appropriate to relate measures of variability to situational variables such as activity. Comparing variability in individuals whose level of physical activity is very different may give spurious results if one is interested in endogenous differences in blood pressure variability. In such instances it may be appropriate to control statistically for the relevant situational variables.

11.4 Analysis of Diurnal Rhythms

The existence of a diurnal rhythm of blood pressure was recognized long before the introduction of ambulatory monitoring. It provides an alternative method for analyzing blood pressure changes, based on the time of day rather than on situational variables such as activity and location. Nevertheless, it is more appropriate to perform the analysis according to the diary data of sleeping and waking rather than any fixed definition of daytime and nighttime, since people go to bed and get up at different times. Since all statistical methods for analyzing time series work best if the data is collected at equal time intervals, the common usage of less frequent readings during the night presents a problem, which may be further exacerbated if there is a large number of missing readings.

11.4.1 Cosinor Analysis

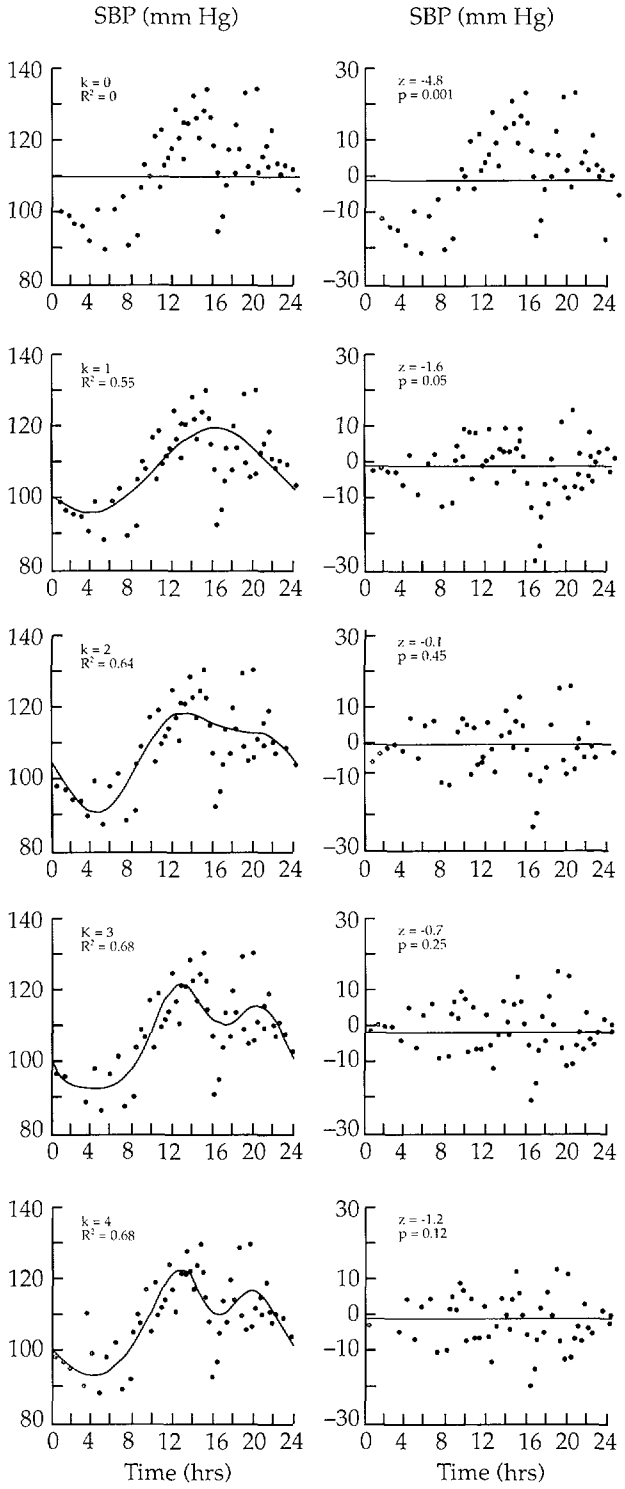
This technique has been widely used for analyzing biological parameters which show as true circadian rhythm (of which blood pressure may or may not be an example). The basic principle is to fit the data to a cosine wave with a periodicity of 24 hours (18,19). The basis for this type of analysis is a three parameter equation of the form:

$$f(t) = a_0 + A\cos(2\pi t + \phi)$$

where
- $f(t)$ = blood pressure at time t
- a_0 = average 24-hour blood pressure
- A = amplitude of the diurnal wave
- ϕ = phase angle (equivalent to the timing of the peak and trough of the wave)

The data points are fitted to the cosine curve by a least squares method that enables the estimation of A and ϕ. This procedure makes the assumption that the peak and trough of the blood pressure are exactly 12 hours apart and equidistant from the mean level (or more precisely, the mesor). Unfortunately, this is rarely the case, so a more empirical if mathematically less pure approach is needed.[329] An example of the relatively poor fit with the data points provided by this type of analysis is shown in Figure 11.7.

Figure 11.7 — Twenty-four-hour blood pressure readings from a normotensive subject (first panel—raw data and mean level) analyzed according to the cosinor method (second panel), and with addition of a second, third, and fourth harmonics by Fourier analysis (third, fourth, and fifth panels, k = 2, 3, and 4). Note progressive improvement of fit. Left set of panels is original data and the right set shows residuals.



11.4.2 Fourier Analysis

Given that a single cosine function may not adequately describe the diurnal rhythm of blood pressure, a more elaborate analysis can be undertaken using a Fourier analysis, which involves adding a series of harmonics with periods such as 12, 8, 6, 4, 3, 2, and 1 hours to the analysis.[330-332] This is likely to provide a better fit to the data than the simpler cosinor analysis, as shown in Figure 11.7.

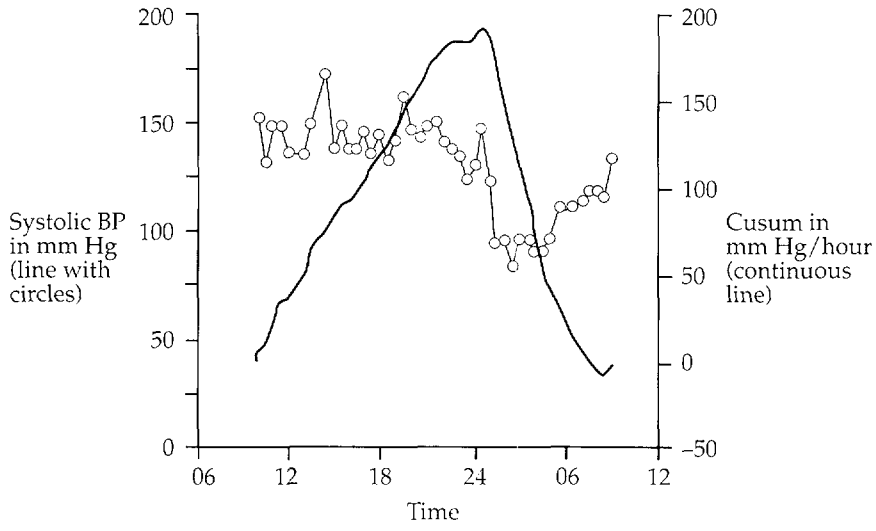
11.4.3 Square Wave Fit

Inspection of individual blood pressure profiles suggests that there is a rather sudden decrease of pressure on going to sleep, and an equally sudden increase on waking. An analysis that assumes that the diurnal profile of blood pressure is, in fact, a square wave with one level of pressure corresponding to wakefulness and the other to sleep found that a greater proportion of the overall variance of pressure could be accounted for than by the cosinor method or Fourier analysis.[333]

11.4.4 Cumulative Sum Analysis

Cumulative sum analysis (Cusum) is a simple and effective technique for identifying the point in time at which a consistent change in a fluctuating variable such as blood pressure first occurs.[334] The deviation of successive points from the average level are summed and plotted, as shown in Figure 11.8. The slope of the line indicates whether you are above or below the 24-hour mean pressure. The method is somewhat similar to the square wave fit in that it gives an estimate of the average difference between the waking and sleeping blood pressures.

Figure 11.8 — Twenty-four-hour systolic blood pressure profile (O) in a hypertensive subject with corresponding cumulative sum (cusum) plot (—).



11.4.5 Analysis Based on Activity

The alternative approach to the analysis of diurnal rhythms is to assume that activity and arousal are the primary determining factors, and to base the analysis on the subject's diary entries.[335,336] In general, two strategies have been employed to assess the effects of activities on blood pressure. The first has been to pool all data from all subjects and then to perform analyses on the entire set of readings. This strategy has the advantage that it is possible to control for confounders and cofactors. Furthermore, individual differences in overall blood pressure level can be allowed for by adjusting for baseline and standardizing the readings before analysis. However, this method is open to criticism because of the variable number of readings per subject, and because it assumes independence of measurements both within and between subjects.

The second strategy has been to calculate the means for each activity separately for each subject. These means are then averaged to arrive at a summary estimate of the effects of the activities in the population. We have also used this method for estimating the effects of situational variables such as work, home, and sleep. While this method is probably more sound statistically, because it does not rest so much on an assumption of independence of observation, it does not control for cofactors and confounders. Furthermore, the differential precision of the estimates for each subject do not allow for the different numbers of readings per subject.

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13.0 ILLUSTRATION CREDITS

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Figure 1.1

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Figure 4.11 and 4.12

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14.0 GLOSSARY

Algorithm — A procedure for solving a mathematical problem in a finite number of steps that frequently involves repetition of an operation.

Antegrade – Moving or extending forward; (or anterograde).

Aorta — The great trunk artery that carries blood from the heart for distribution by the branch arteries throughout the body.

Ambulatory blood pressure monitoring — A means to measure blood pressure over a period of time.

Apnea syndrome — Episodic and repetitive apneic episodes occurring throughout the night; mainly affects middle-aged men.

Area under the curve — Traditional method of quantifying the effects of a drug on blood pressure which compares the area of the plot of blood pressure against time with and without the drug.

Arrhythmia — An alteration of either time or force of the rhythm of the heart beat.

Arteriole — One of the small endings of an artery that leads into capillaries.

Artery — A vessel or tube-like structure through which blood passes away from the heart to various parts of the body.

Artifact — Any structure or feature that is not normal or natural; e.g., distortions, aberrations, and inaccuracies of the normal blood pressure waveform.

Arteriosclerosis — A group of diseases characterized by thickening and loss of elasticity of arterial walls.

Atria — Plural for atrium (see definition below).

Atrioventricular valves — Valves located between the cavities of the atrium and ventricle in each half of the heart; which permits blood to flow from the atrium to the ventricle, but not from the ventricle to the atrium.

Atrium — A chamber; used in anatomical nomenclature to designate a chamber allowing entrance to another structure or organ; usually used alone to designate a chamber of the heart.

Auricle — The chamber(s) of the heart that receives blood from the veins and forces it into the ventricle(s). Used most commonly in reference to nonhuman anatomy.

Auscultate — To examine by listening, usually to the sounds of the thoracic or abdominal viscera with or without a stethoscope.

Auscultation — The act of listening for sounds within the body, chiefly for ascertaining the condition of the heart or other organs.

Auscultatory — Of or pertaining to auscultation; a noninvasive method of blood pressure measurement.

A-V valves — See atrioventricular valves.

Beta blockers — A substance that interferes with the transmission of stimuli through pathways that normally allow sympathetic nervous inhibiting stimuli to be effective.

Blood pressure — The pressure exerted by the blood on the wall of any vessel.

Capillaries — Any of the smallest vessels of the vascular system that connects an arteriole with a venule to complete the formation of blood vessel networks throughout the body.

Cardiac — Pertaining to the heart.

Cardiac cycle — The period from the end of one heart contraction to the end of the next contraction. The cardiac cycle consists of a period of relaxation called diastole followed by a period of contraction called systole.

Cardiac output — The volume of blood pumped by each ventricle per minute, usually expressed as liters per minute (L/m). Cardiac output is determined by multiplying the heart rate and the volume of blood ejected by each ventricle during each heart beat (stroke volume) [Cardiac output = heart rate X stroke volume].

Casual blood pressure — The noninvasive measurement of blood pressure in a home, clinic, or hospital setting.

Catheter — A tubular medical device for inserting into canals, vessels passageways, or body cavities to permit injection or withdrawal of fluids, to keep passages open, or to measure an internal body parameter.

Compliance — A quality of yielding to pressure or force without disruption, or an expression of the measure of the ability to do so, as an expression of the distensibility of an air- or fluid-filled organ, e.g., the lung or urinary bladder, in terms of unit of volume change per unit of pressure change.

Chronic renal disease — Disease process that causes decreased ability of the kidneys to perform their function of excreting urine and helping regulate the water, electrolyte, and acid-base content of the blood.

Diastasis — The middle third of diastole when the inflow of blood into the ventricles has nearly stopped; the rest period of the cardiac cycle that occurs just before systole.

Diastole — The dilatation or period of dilatation of the heart, especially of the ventricles; diastole coincides with the interval between the second and first heart sounds.

Diastolic — Of or pertaining to diastole.

Dicrotic — Having a double beat; related to the sound expansion of the artery that occurs during the diastole of the heart.

Dilation — The action of dilating or stretching.

Dilatation — The condition of being dilated or stretched beyond the normal dimensions; e.g., the act of dilating or stretching an orifice or tubular structure.

Dippers and nondippers — Sustained hypertension may be subdivided in those who show a normal nocturnal fall of pressure—dippers—and those whose pressure remains high—nondippers.

Distal — Remote; farther from any point of reference; opposed to proximal.

Diurnal — In or of the daytime.

End-diastolic volume — The amount of blood in the ventricle just prior to systole.

Frequency — The number of occurrences of a periodic process in a unit of time; the number of vibrations made by a particle or ray in 1 second; in electricity, the rate of oscillation or alternation in an alternating current.

Frequency response – The upper and lower frequencies at which the amplitude response has fallen to 3 decibels below the midfrequency value.

Hawksley — A random zero sphygmomanometer.

Heart failure — A clinical syndrome characterized by distinctive symptoms and signs resulting from disturbances in cardiac output or from increased venous pressure. Most often applied to myocardial failure, with increased pressures distending the ventricle (high end-diastolic pressure) of the heart and a cardiac output inadequate for the body's needs; often subclassified as right- or left-sided heart failure depending on whether the systemic or pulmonary veins are predominantly distended.

Hemodynamics — The study of movements of the blood and of the forces associated with the blood system.

Hertz — A unit of frequency equal to 1 cycle per second; abbreviated Hz.

Home blood pressure — The noninvasive measurement of blood pressure in a home setting using a retail blood pressure device.

Hydrostatic — Pertaining to a liquid in a state of equilibrium.

Hydrostatic pressure – The pressure at any level on water (or blood) at rest due to the weight of the water (or blood) above it.

Hypertension — Persistently high arterial blood pressure.

Hypertrophic — Pertaining to or marked by hypertrophy.

Hypertrophy — The enlargement or overgrowth of an organ or part due to an increase in size of its constituent cells.

Hypotension — Abnormally low blood pressure; seen in patients in shock but not necessarily indicative of this condition.

Interstitial — Pertaining to or situated between parts or in the interspaces of a tissue.

Intra-arterial blood pressure — Measurement of blood pressure via a catheter into an artery. The catheter is usually coupled via a fluid-filled tube to a pressure transducer outside the body.

Intrapleural space — The space within the pleura (see definition below).

Isometric — Maintaining or pertaining to the same measure of length; of equal dimensions; not isotonic.

Isovolumetric contraction — The first phase of ventricular systole; begins with the closure of the atrioventricular valve and ends with the opening of the semilunar valve. Tension increases in the muscle but shortening of the muscle fiber does not occur.

Isovolumetric relaxation — The first phase of ventricular diastole; begins with the closure of the semilunar valve (see definition below) and ends with the opening of the antrioventricular valve.

Korotkoff sounds — Noises created by the spurting blood from the compressed brachial artery which produce turbulence and vibrations within the vessel.

Left ventricular hypertrophy — Increase in size of the left ventricular tissue without increase in size of cavity.

Malignant hypertension — Hypertension that is getting worse, and immediate treatment is of the highest priority.

Mayer waves — Periodic waves of blood pressure which are slower than the respiratory oscillations and which may be mediated via the chemoreceptors. Mayer waves have a periodicity of 0.07 Hz to 0.12 Hz and can be seen quite clearly during apneic episodes.

Mean pressure — The average of all values of pressure observed at the measurement site over a number of cardiac cycles.

Mitral valve — A cardiac valve that consists of two triangular flaps and guards the orifice between the left atrium and ventricle; also called the bicuspid valve.

Morbidity — The state of being diseased. The number of sick persons or cases of disease in relationship to a specific population.

Myocardium — The middle and thickest layer of the heart wall; composed of cardiac muscle.

Normotension — Normal blood pressure.

Office hypertension — See white coat hypertension.

Oscillometric technique — The principle that as an occluding cuff deflates from a level above systolic pressure, the artery walls begin to vibrate or oscillate as the blood flows; these vibrations will be sensed in the transducer system monitoring cuff pressure.

Palpation — The act of feeling with the hand; the application of the fingers with light pressure to the surface of the body to determine the consistence of parts beneath the surface in a physical examination.

Pericardial — Pertaining to the pericardium (see definition below).

Pericardium — The fibroserous sac that surrounds the heart and the roots of the great vessels, comprised of an external layer of fibrous tissue and an inner serous layer. The base of the pericardium is attached to the central tendon of the diaphragm.

Peripheral resistance — The resistance to the passage of blood through the small blood vessels, especially the arterioles.

Peripheral resistance unit — The unit used to measure resistance in a blood vessel, usually given in milliliters (mL) of mercury per milliliter (mL) per minute.

Phlebostatic axis — The reference point for human blood pressure measurement; located at the level of the atria.

Pleura — The serous membrane investing and interspersed throughout the lungs and lining of the thoracic cavity, completely enclosing a potential space know as the pleural cavity. Two distinct pleurae exist, right and left, both of which are moistened with a serous secretion that facilitates the movements of the lungs in the chest cavity.

Pre-eclampsia — A toxemia of pregnancy characterized by increasing hypertension, headaches, albuminuria, and edema of the lower extremities.

Primigravid — A woman during her first pregnancy.

Protodiastole — Early diastole; the period of slow ejection during the ventricular cycle.

Proximal — Nearest; closer to any point of reference; opposed to distal.

Pseudohypertension — False hypertension that results from rigidity of the brachial artery causing resistance to compression by the sphygmomanometer cuff (seen in elderly patients).

Pulse pressure — The difference between the systolic and diastolic pressures.

REM sleep — Cyclic movement of the closed eyes observed or recorded during sleep.

Resistance — Opposition or counteracting force; an impediment to blood flow in a vessel.

Retrograde — Going backward; retracing a former course.

S-A node — See sinoatrial node.

Secondary hypertension — Next to or following; second in order, i.e., hypertension is a secondary sign of pre-eclampsia, but is important as it is an early indication of the disease and a key diagnostic sign.

Semilunar valve — A valve having semilunar (resembling a crescent or half-moon) cusps; for example, the aortic valve and the pulmonic valve.

Septum — A dividing wall or partition.

Sinoatrial node — A microscopic collection of atypical cardiac muscle fibers at the superior end of the sulcus terminalis and at the junction of the superior vena cava and right atrium; also called sinus node. The cardiac rhythm normally begins at the sinoatrial node so that this node is also know as the pacemaker of the heart.

Stoke volume — The amount of blood ejected from a ventricle at each beat of the heart.

Systole — The contraction, or period of contraction, of the heart, especially that of the ventricles. Systole coincides with the interval between the first and second heart sound during which blood is forced into the aorta and the pulmonary trunk.

Systolic — Pertaining to or produced by the systole; occurring along with the ventricular systole.

Tachycardia — Relatively rapid heart action.

Target organ — The organ or structure toward which the effects of a drug, hormone, or therapeutic agent are primarily directed.

Transducer — A device that converts fluid pressures to electrical voltages. Standardized transducers are interchangeable because they generate the same amount of voltage output per unit of fluid pressure applied. The resting output voltage of the transducer is know as the offset with, the atmospheric pressure applied to the sensing membrane which is often some other value that 0 volts.

Tricuspid valve — This valve is composed of three flaps that prevent the reflux of blood from the right ventricle to the right atrium.

True blood pressure — A conceptual rather than an actual measurement; the average or usual level of pressure for a particular individual.

Ultradian rhythms — Biologic rhythms that occur less frequently than every 24 hours.

Vasoconstriction — The lowering of the caliber of blood vessels, especially the tightening or constriction of the arterioles, leading to decreased blood flow to that body part.

Vasodilation — Dilation or opening up of a blood vessel, especially of the arterioles leading to increased blood flow to that body part.

Ventricle — A chamber of the heart that receives blood from a corresponding atrium and from which blood is forced into the arteries.

Venae cava — The vena cava inferior and superior (see definitions below).

Vena cava inferior — The venous trunk for the lower extremities and for the pelvic and abdominal viscera; it begins at the level of the fifth lumbar vertebra where the common iliac veins unite, passes upward on the right of the aorta, and empties into the right atrium of the heart.

Vena cava superior — Venous trunk draining blood from the head, neck, upper extremities, and chest; it begins where the two brachiocephalic veins unite, passes directly downward, and empties into the right atrium of the heart.

Venule — A small vein; especially one of the minute veins connecting the capillary bed with the larger systemic veins.

Volumetric compliance — The amount of volume increase per unit of applied pressure in the catheter pickup system; usually due to elasticity of components.

White coat hypertension — The general tendency for clinic pressures to overestimate the true blood pressure. Any individual whose blood pressure tends to increase in the presence of a clinician.

Windkessel model — The simplest model of the arterial tree which can be likened to an expansible chamber (the large arteries) into which the heart pumps, with a narrow outlet of variable resistance (the arterioles).

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